Formulation performance in paediatric patients - in vitro predictive models and biowaivers

Martir, Joana

Award date:
2019

Awarding institution:
University of Bath

Formulation performance in paediatric patients - *in vitro* predictive models and biowaivers

Joana Filipa Loulé Mártir

A thesis submitted for the degree of Doctor of Philosophy

University of Bath

Department of Pharmacy and Pharmacology

April 2019

Table of Contents

Acknowledgements

I would like to express my gratitude to my lead supervisor, Dr. Nikoletta Fotaki, for the opportunity, guidance and continuous support throughout my studies.

I would also like to thank Dr. Talia Flanagan and Dr. James Mann for their supervision and support.

I gratefully acknowledge the University of Bath and AstraZeneca (UK) for kindly funding this project.

Many thanks to Fotios Baxevanis, John Nikolettos and Sarah Cordery for their time, guidance and support in the beginning of my Ph.D. Thanks to Ricardo Diaz de Leon Ortega for his support and time spent helping me with my statistical analyses.

Also, thanks to Alice Tabosa, Mariana Correia and Angela Effinger for their friendship and company along the way. Special thanks to Mariana and Simon Vanstone for their precious help in the last few months of my Ph.D.

Thank you Sally for the constant encouragement and company during these years.

Finally, many thanks to my wonderful parents for their love, encouragement and constant support: Obrigada por tudo o que fazem por mim.

Publications and Conference Contributions

Publications (peer-reviewed journals)

Martir J, Flanagan T, Mann J, Fotaki N. Recommended strategies for the oral administration of paediatric medicines with food and drinks in the context of their biopharmaceutical properties: a review. J Pharm Pharmacol. 2017;69(4):384-97.

Plan for future publications

Chapters 2 – 6 will be submitted as research papers in peer-reviewed journals.

Conference contributions

Martir J, Flanagan T, Mann J, Fotaki N. Characterisation of the physicochemical properties of food and drinks used for the co-administration of drugs in the paediatric population. 2017. Abstract and poster presentation: AAPS annual meeting, San Diego, USA.

Martir J, Flanagan T, Mann J, Fotaki N. Impact of co-administration of food and drink vehicles on the solubility of poorly soluble paediatric drugs. 2017. Abstract and poster presentation: AAPS annual meeting, San Diego, USA.

Martir J, Flanagan T, Mann J, Fotaki N. Stability of paediatric drugs co-administered with different foods and drinks. 2017. Abstract and poster presentation: AAPS annual meeting, San Diego, USA.

Martir J, Flanagan T, Mann J, Fotaki N. Effect of co-administration of foods and drinks on the dissolution of paediatric formulations – case study montelukast. 2018. Abstract and poster presentation: AAPS PharmSci 360, Washington DC, USA.

Martir J, Flanagan T, Mann J, Fotaki N. Effect of co-administration of foods and drinks on the dissolution of paediatric formulations – case study mesalazine. 2018. Abstract and poster presentation: AAPS PharmSci 360, Washington DC, USA.

List of tables

List of figures

Figure 3.6. Solubility of montelukast and mesalazine (top and bottom sections, respectively) in the different drink and food vehicles, obtained after 4h (plot and whiskers) and 24h (floating bars); values shown represent the 3 replicates measured. Each set of colours represents a subtype of vehicles.

Figure 3.7. Solubility values (logarithmic scale) of montelukast and mesalazine in the selected media (soft foods, drinks) *vs* (a) pH (including solubility in buffers) (2D plot), and *vs* (b) pH and viscosity, (c) pH and % of fat, (d) pH and % of protein, and (e) pH and % of sugars (3D scatter plots).

Figure 3.8. Standardised coefficients corresponding to the variables and interactions studies for the solubility of montelukast (a, b) and mesalazine (c, d), at 4 h (left panel; a, c) and 24 h (right panel; b, d). Blue and red colours denote coefficients with a significant impact on the solubility of montelukast and mesalazine, respectively (VIP >1; data not shown). [BC = buffer capacity; ST = surface tension].

Figure 4.1. Mean % montelukast dissolved (± S.D.) from Singulair® granules (top panel) and Actavis® chewable tablets (bottom panel) after direct administration of formulation, after mixing with selected vehicles (full lines) and with vehicles of the same subtype (dashed lines). Dotted vertical lines represent the time of medium change.

Figure 4.2. Effect of co-administration of formulation with vehicles on % of drug dissolved at 4 h from the tested formulations. * denotes a statistical difference on drug dissolution between direct administration (dashed line) and co-administration with vehicles (bars; red: drinks, blue: soft foods). *a* denotes statistical difference when vehicles of the same subtype were tested ($p < 0.05$).

Figure 4.3. Mean % mesalazine dissolved (± S.D.) from Pentasa® (top panel) and Salofalk® granules (bottom panel) after direct administration of formulation, after mixing with selected vehicles (full lines) and with vehicles of the same subtype (dashed lines). Dotted vertical lines represent the time of medium change.

Figure 4.4. Effect of co-administration of formulation with vehicles on % of drug dissolved at 4 h from the tested formulations. * denotes a statistical difference on drug dissolution between direct administration (dashed line) and co-administration with vehicles (bars; red: drinks, blue: soft foods). *a* denotes statistical difference when vehicles of the same subtype were tested ($p < 0.05$).

Figure 4.5. Mean % montelukast dissolved (± S.D.) from Singulair® granules (top panel) and Actavis® chewable tablets (bottom panel), under two administration scenarios: testing immediately after mixing (dashed lines) and 4 h after mixing (full lines). Dotted vertical lines represent the time of medium change.

Figure 4.6. Effect of a 4 h delay between mixing and testing of formulation with vehicles on drug dissolution from the tested formulations. * denotes a statistical difference on drug dissolution between testing immediately after mixing (dashed bars) and testing 4 h after mixing (full bars).

Figure 4.7. Mean % mesalazine dissolved (± S.D.) from Pentasa® granules (top panel) and Salofalk® granules (bottom panel) under two administration scenarios: testing immediately after mixing (dashed lines) and 4 h after mixing (full lines). Dotted vertical lines represent the time of medium change.

Figure 4.8. Effect of a 4 h delay between mixing and testing of formulation with vehicles on drug dissolution from the tested formulations. * denotes a statistical difference on drug dissolution between testing immediately after mixing (dashed bars) and testing 4 h after mixing (full bars).

Figure 4.9. Mean % drug dissolved (± S.D.) of montelukast from Singulair® granules (top panel) and mesalazine from Pentasa® granules (bottom panel), after testing under two agitation rate conditions: 50 rpm (dashed bars) and 100 rpm (full bars). Dotted vertical lines represent the time of medium change.

Figure 4.10. Effect of dissolution hydrodynamics on $AUC_{0\text{-}4h}$ of Singulair® (montelukast) and Pentasa® (mesalazine) granules. * denotes a statistical difference in $AUC_{0\text{-}4h}$ between drug dissolution when agitation rate was set at 50 (dashed bars) and 100 rpm (full bars).

Figure 4.11. Standardised coefficients corresponding to the variables studied for dissolution of montelukast, mesalazine and both drugs. Colour denotes coefficients with a moderate (lighter colour) and significant (darker colour) impact on the response (VIP > 0.7 and 1, respectively). [B.C. = buffer capacity; ST = surface tension]

Figure 5.1. Mean % montelukast dissolved (± S.D.) from Singulair® granules and Actavis® chewable tablets after direct introduction of the formulation and mixing with selected vehicles, under fasted gastric conditions, followed by fasted (full lines)

or fed (dashed lines) intestinal conditions. Dotted vertical lines represent the time of medium change.

Figure 5.2. $AUC_{0\text{-}4h}$ *in vitro* (% dissolved*h) of montelukast dissolution profiles after direct administration of formulation and after mixing with the vehicles. *a* denotes statistical difference between direct administration (blue bars) and co-administration with vehicles (other colours); * denotes a statistical difference on drug dissolution between testing under fasted gastric conditions, followed by fasted (dashed bar) or fed (full bar) intestinal conditions ($p < 0.05$).

Figure 5.3. % of montelukast absorbed *in vivo* after administration of Singulair® granules (4 mg) to: (a) 1 to 3 months infants with formula (15); (b) 3 to 6 months infants with applesauce (14); and (c) 6 to 12 months infants with applesauce (17). The % absorbed was calculated with the Wagner–Nelson equation.

Figure 5.4. Ratio (%) between each $AUC_{0\text{-}4h}$ *in vitro* and $AUC_{0\text{-}4h}$ *in vivo* ($AUC_{0\text{-}4h}$ *in vitro*/$AUC_{0\text{-}4h}$ *in vivo* x 100) for: (a) *in vitro* fasted gastric followed by fasted intestinal conditions; and (b) *in vitro* fasted gastric followed by fed intestinal conditions. Grey area represents the range criteria (80 – 125 %) set for prediction of *in vivo* drug performance.

Figure 6.1. Schematic representation of the different dissolution setups tested: (1) 900 mL, USP II apparatus; (2) 250 mL, USP II apparatus; (3) 50 mL, mini-paddle apparatus.

Figure 6.2. Mean % amoxicillin dissolved (± S.D.) from Amoxil® capsules 250 mg (full lines) and 500 mg (dashed lines), in acetate buffer pH 4.5 (top) and phosphate buffer pH 6.8 (bottom), under two testing scenarios: setup 1 (USP II apparatus, 900 mL) and setup 2 (USP II apparatus, 250 mL) (left and right panels, respectively). Three agitation rates were tested: 50 rpm (blue), 75 rpm (red) and 100 rpm (black).

Figure 6.3. Mean % amoxicillin dissolved (± S.D.) from Amoxil®, amoxicillin Teva® and amoxicillin Kent® capsules 250 mg (left panels) and 500 mg (right panels), in SGF*sp* pH 1.2 (blue), acetate buffer pH 4.5 (green) and phosphate buffer pH 6.8 (red). Three setup scenarios were tested: (1) 900 mL, USP II apparatus; (2) 250 mL, USP II apparatus; (3) 50 mL, mini-paddle apparatus (from top to bottom). Dotted grey lines represent the limit for '*very rapid dissolution*' classification (> 85 % dissolved within 15 min).

Figure 6.4. Mean % prednisolone dissolved (± S.D.) from Pevanti® and prednisolone Actavis® tablets 5 mg (left panels) and 25mg (right panels), in SGFsp pH 1.2 (blue), acetate buffer pH 4.5 (green) and phosphate buffer pH 6.8 (red). Three setup scenarios were tested: (1) 900 mL, USP II apparatus; (2) 250 mL, USP II apparatus; (3) 50 mL, mini-paddle apparatus (from top to bottom). Dotted grey lines represent the limit for 'very rapid dissolution' classification (> 85 % dissolved within 15 min).

Figure 6.5. Mean % amlodipine dissolved (± S.D.) from Istin®, amlodipine Sandoz® and amlodipine Teva® tablets 5 mg (left panels) and 10 mg (right panels), in SGF*sp* pH 1.2 (blue), acetate buffer pH 4.5 (green) and phosphate buffer pH 6.8 (red) under three testing scenarios. Three setup scenarios were tested: (1) 900 mL, USP II apparatus; (2) 250 mL, USP II apparatus; (3) 50 mL, mini-paddle apparatus (from top to bottom). Dotted grey lines represent the limit for '*very rapid dissolution*' classification (≥ 85 % dissolved within 15 min).

Figure 6.6. Risk assessment of extending the biowaiver for IR formulations of 3 model compounds from the adult to the paediatric population. (N/A: not applicable). Green and red colours represent if the products would pass or fail, respectively, the rapid dissolution criteria. [(+): follows the criterion; (-): fails the criterion]

Abbreviations and glossary of terms

ANOVA	Analysis of variance
API	Active principal ingredient
AUC	Area under the concentration-time curve
$AUC_{0\text{-}4h}$	Area under the curve from time 0 extrapolated to time 4 h
BA	Bioavailability
BCS	Biopharmaceutics classification system
BCPA	Best Pharmaceuticals for Children Act
BE	Bioequivalence
BNF-C	British National Formulary for Children
CD-P-PH	European Committee on Pharmaceuticals and Pharmaceutical Care
C_{max}	Maximum plasma concentration
D_0	Dose unit
EDQM	European Directorate for the Quality of Medicines & HealthCare
EMA	European Medicines Agency
f_2	Similarity factor
FaSSIF-V2	Fasted-state Simulated Intestinal fluids (version 2)
FDA	Food and Drug Administration
GF/D	Glass microfiber
GI	Gastrointestinal
GR	Gastro-resistant
HPLC-UV	High-performance liquid chromatography with ultraviolet detection
HSD	Honestly significant difference
IR	Immediate release
IVIVC	*In vitro-in vivo* correlation
IVIVR	*In vitro-in vivo* relationship
logP	log (octanol/water partition coefficient)
MR	Modified release
p-BCS	Paediatric biopharmaceutics classification system
PD	Pharmacodynamics
Pi-FaSSGF	Paediatric Fasted State Simulated Gastric Fluid, representative of infants
Pi-FeSSIF	Paediatric Fed State Simulated Gastric Fluid, representative of infants
PIL	Product information leaflet

PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
PLS-R	Partial least squares regression
PRESS	Predicted residual error sum of squares
PTFE	Polytetrafluoroethylene
PUMA	Paediatric Use Marketing Authorisation
Q^2	Goodness of prediction
R^2	Coefficient of determination
RC	Regenerated cellulose
RPM	Revolutions per minute
S.D.	Standard deviation
SGF*sp*	Simulated gastric fluid *sine pepsin* (without enzymes)
SIF	Simulated intestinal fluid
SmPCs	Summary of product characteristics
$T_{1/2}$	Half-life time
TFA	Trifluoroacetic acid
T_{max}	Time to reach maximum plasma concentration (C_{max})
UK	United Kingdom
USA	United States of America
USP	United States Pharmacopoeia
UV	Ultraviolet
V_0	Initial gastric volume
VIP	Variable importance in projection

Abstract

The field of paediatric biopharmaceutics is currently evolving, as a result of the distinct needs of this population regarding formulation design and performance. Age-appropriate biopharmaceutical tools for paediatric formulation development are warranted due to their potential in minimising scientific and regulatory risks.

The aim of this thesis was to develop *in vitro* predictive tools to aid understanding of formulation performance in paediatrics, with emphasis on co-administration of medicines with food and drinks (vehicles), and to explore the extension of the Biopharmaceutics Classification System (BCS) to paediatrics. Common practices of medicine co-administration with vehicles were investigated and compared with the relevant guidelines. The possible negative outcomes of this practice were highlighted, revealing the need for a unified mandatory guidance on administration practices, vehicle selection and assessment. Frequently recommended vehicles were selected, and their physicochemical properties and composition were characterised. These differences had an impact on the solubility of two poorly soluble drugs, montelukast and mesalazine. Age-appropriate *in vitro* dissolution testing was developed to predict the impact of medicine co-administration on drug product performance. Drug dissolution was affected by co-administration with food and drinks in comparison to direct administration of formulation, and the time between preparation and testing of the drug-vehicle mixture. A biorelevant dissolution testing setup was developed, which predicted the *in vivo* formulation performance after medicine co-administration with vehicles in infants. Ultimately, the potential of dissolution studies with mini-paddle in mimicking paediatric administration practices and predicting *in vivo* drug performance was shown. An extension of current BCS-based biowaiver criteria into paediatrics was explored but shown not to be feasible due to gaps in knowledge regarding the gastrointestinal tract of paediatric patients, which hinder the development of a paediatric-BCS.

Overall, this thesis provides a useful insight on the critical aspects of paediatric biopharmaceutics, with an overview on the possible impact of administration practices on paediatric clinical outcomes. This could be a starting point towards developing physiologically relevant *in vitro* biopharmaceutical tools, which can be used to assess product drug performance in paediatric subpopulations.

Aims and objectives

This thesis discusses the benefit of developing appropriate biopharmaceutical tools for paediatric formulation development in order to minimise scientific and regulatory risks. The overall aim of this project was to develop predictive tools to understand formulation performance in the paediatric population, by gaining a biopharmaceutical understanding of current paediatric medicine co-administration practices and how these may impact therapy, and to identify the gaps in existing biopharmaceutical knowledge in this population. Age-appropriate biorelevant *in vitro* dissolution tests were developed to predict the impact of administration practices and age factors on drug product performance.

The specific objectives of each chapter were:

Chapter 1: To provide a general overview of the current strategies employed to overcome administration of a specific dose, acceptability and adherence issues of medicines in the paediatric population, with focus on the co-administration of medicines with food and drinks (vehicles). More specifically, an insight was given on the strategies for the co-administration of medicines with vehicles in the UK, in the context of their biopharmaceutical properties. Current administration practices reported by healthcare professionals and parents/carers were compared with the relevant guidelines, setting the background and experimental challenges of the Ph.D. project.

Chapter 2: To describe the current recommended strategies for paediatric co-administration of medicines with vehicles. Current administration recommendations in different settings were compared in order to obtain a global respective on practices and recommendations. A statistical model was developed to understand the rationale behind vehicle selection based on drug and formulation properties.

Chapter 3: To screen the physicochemical properties of a selection of soft food and drinks, commonly reported to be mixed with medicines prior to paediatric administration, and to evaluate the vehicle-impact on the solubility of two poorly soluble drugs, montelukast and mesalazine. More specifically, in this chapter the importance of evaluating the possible vehicle-effect on drug solubility and, ultimately, product drug performance was highlighted.

Chapter 4: To develop an *in vitro* dissolution testing setup which could be used to evaluate drug dissolution whilst addressing typical dosing conditions, such as the effect of medicine co-administration with vehicles. The effect of medicine co-administration with selected foods and drinks, and of different administration practices on drug dissolution was then evaluated. This study was used to demonstrate the potential of *in vitro* dissolution studies in mimicking administration practices and predicting formulation performance in the paediatric population.

Chapter 5: To develop a predictive, biorelevant *in vitro* dissolution test to investigate the impact of practices of medicine co-administration with vehicles on the dissolution performance of a poorly soluble compound. To predict *in vivo* formulation performance, paediatric biorelevant media was used in combination with the dissolution setup developed in Chapter 4 to simulate the *in vivo* gastrointestinal environment of infants. Based on the *in vitro* dissolution data and the *in vivo* data available in the literature, *in vitro-in vivo* relationships were obtained.

Chapter 6: To assess the risk of extending Biopharmaceutics Classification System (BCS)-based biowaiver criteria into paediatric products. Compounds that would change drug solubility class in the paediatric population were identified and their immediate release formulations were tested. The performance of the formulations tested in age-appropriate conditions were evaluated in order to identify bioinequivalence risks.

Chapter 1: Recommended strategies for the oral administration of paediatric medicines with food and drinks in the context of their biopharmaceutical properties: a review

Abstract

Objectives: This review focuses on the recommended strategies for the oral administration of paediatric medicines with food in the context of their biopharmaceutical properties.

Key findings: Acceptability of oral medicines in young patients is more challenging than in adult patients. Mixing oral dosage forms with foods and drinks is sometimes suggested in order to administer a specific dose and enhance compliance in the paediatric population. In this review, the strategies for the co-administration of paediatric medicines with food and drinks are discussed. Current administration practices as reported by healthcare professionals and parents/carers are compared with the relevant guidelines. Differences in the type of vehicles recommended to be used and actually used in current practice were identified. Correlations of the type of food recommended the type of formulation and the drug's Biopharmaceutical Classification System (BCS) class were performed and revealed that recommendations should be made on a case-by-case basis.

Summary: The propensity for physiochemical or bioavailability changes that may occur from the co-administration of medicines with food and drinks in the paediatric population should be considered and harmonisation of the recommended administration strategies is needed.

1. Introduction

Historically, medicines for children have not been designed and tested for each target subpopulation. Medicines developed for adults are commonly administered to the paediatric population, usually informally adapted and in the absence of relevant evidence (1). It is widely recognised though that 'Children are not just small adults'(2); constant developmental changes, in terms of anatomical and physiological aspects until adulthood, need to be considered for an efficient treatment and the development of appropriate formulations.

The use of unlicensed and off-label medicines for children is widespread, with healthcare professionals, parents or carers facing the need to manipulate medicines designed for adults (3). This manipulation that can range from simple (*e.g.* tablet splitting) to complex methods (*e.g.* tablet crushing for suspension preparation) results in the availability of formulations ready to be administered and appropriate for the condition and patient intended. Appropriate oral formulations for young patients need to overcome swallowing difficulties or undesirable palatability, which could affect adherence in these patients (3-6).

Acceptability, defined as the overall acceptance of the dosage form regardless of the mode of its administration (7), has been identified as an integral part of the paediatric formulation development. It depends on several factors, such as suitability of the dosage form and palatability of the oral medicine. Palatability, described as the overall acceptance of the taste, flavour, smell, dose, volume or size, and texture of a medicine to be administered by mouth or to be swallowed, is essential for adherence in this population and influences the choice of dosage form and its design (7). Carers usually attempt to facilitate administration and improve the acceptance of the patient by mixing the dose with food or drinks (8, 9). If this situation is intended/predicted, appropriate compatibility studies should be conducted to evaluate possible changes in bioavailability and information should be provided in the patient information leaflet, by the manufacturer (3). Recent studies have shown that sometimes this type of co-administration is performed without following the appropriate procedures, for example, by letting the child or carer chose the food or drink used for administration without proof of safety and efficacy (8, 9).

This review describes the current strategies employed to overcome administration of a specific dose, acceptability and adherence issues of medicines in the paediatric population, focusing on the co-administration of medicines with food and drinks. Current administration practices as reported by healthcare professionals and parents/carers are compared with the relevant guidelines in order to assess the possible clinical consequences of these practices, in particular changes in the bioavailability of the drug. The type of food and drinks co-administrated with paediatrics medicines was correlated with the type of formulation and the drug's Biopharmaceutical Classification System (BCS) class in order to reveal the biopharmaceutical aspects of the recommended administration strategies.

2. Age classification of paediatric patients

Children differ from adults from a biological and pharmacological development perspective, and these differences should be reflected in the development and use of medicines for the paediatric population. Moreover, and although often overlooked, due to continuous physiological growth and maturation, the paediatric population is not a homogeneous group and can be subdivided accordingly to specific age groups. The division of this population in specific age groups is not harmonised between all the regulatory authorities, and some differences are observed in the upper age limit and in the distinction between young children and older children and premature and term newborns (10-12). In this review, the classification identified by the International Conference on Harmonization of Technical Requirements for registration of Pharmaceuticals for Human Use (10) is followed (Table 1.1).

Table 1.1. Paediatric age sub-groups (10)

Paediatric sub-group	Name used	Age
Preterm newborn infants ('Prematures')		<37 weeks gestation
Term newborn infants ('Neonates')	Neonates	0-27 days
Infants and toddlers	Infants	28 days-24 months
Children	Children	2-11 years
Adolescents	Adolescents	12-16 or 18 years (depending on region)

3. Paediatric formulations: from regulatory guidance to reality

3.1 Regulatory status

Developing paediatric formulations as acceptable dosage forms, with a predictable and safe drug release in the patient and ensuring compliance, is scientifically challenging due to unique requirements and limitations (1, 13). The paediatric population represents a small target group with many short-term illnesses, and the development of acceptable formulations can differ significantly from the adult formulations in terms of the excipients that can be used and the selected route of administration (5, 13).

New regulations, additional funding opportunities and innovative collaborative research initiatives both in the USA (Best Pharmaceuticals for Children Act – BPCA, and the Pediatric Research Equity Act – PREA (14, 15)) and the European Union ('Better medicines for children' concept paper and the Paediatric Regulation (EC) N°1901/2006, which introduced Paediatric Use Marketing Authorization – PUMA – and Paediatric Investigation Plan – PIP (1, 16)), have affected the paediatric formulation development. Novel formulations, such as flexible, dispersible, and multiparticulate oral solid dosage forms start to appear. The paradigm shift towards oral solid formulations of appropriate size and properties (i.e. sprinkles, multiparticulates) has enabled greater dose flexibility, easier administration and better acceptability of drug formulations, whilst efficacy and safety are maintained. Overcoming swallowability and taste and texture issues of the drug formulation is a current challenge in order to achieve paediatric compliance (5). Co-administration with food and drinks is often recommended to facilitate ingestion but it may have an impact on the solubility and oral bioavailability of the drug, and the risk of medication errors is increased (9, 17, 18).

The European Medicines Agency highlights the need for appropriate testing to support formulation changes during paediatric formulation development, the importance of changes in bioavailability when extemporaneously manipulating a solid dosage form by mixing with food and drinks, and the impact of physiology on the absorption potential from modified release formulations (7). Furthermore, any formulation changes undertaken for the development of an acceptable and safer or

more effective formulation for different paediatric age groups should be included in the paediatric investigation plan (19).

Legislative and regulatory frameworks, which underpin the expectation that children will be given the medicines they deserve, have been established in two major jurisdictions (EU and USA). However, scientific evidence in order to guide paediatric formulation development is still lacking, with data and experience acquired by individual pharmaceutical companies during product development not being always available in the public domain.

3.2 Use of off-label and unlicensed medicines in the paediatric population

The frequency of use of off-label and unlicensed medicines in children in the United Kingdom (UK) is ~ 11 % in general practice (20), 25 % in hospital general wards (21), 40 % in paediatric intensive care units (22) and 80 % in neonatal intensive care units (23). This trend is similar in other European countries (24, 25).

Most of the authorised medicines are intended for adult use and are usually available as tablets (single or multiple unit) or capsules. Children are not always able to take the dosage forms that are designed for adults; for example, tablets for adults may need to be split before being administered to younger children, leading sometimes to unevenly tablet splitting and consequent dosage variability when the tablet design is not appropriate for this practice. In cases of liquid formulations for adults, their concentration may not permit the administration of the correct paediatric dose; for example, when the drug concentration of a liquid formulation is high, the volume needed to prepare the paediatric dose is extremely low and difficult to measure and administer. Dosage flexibility and ease of administration are essential as the dose administered throughout childhood relates to body weight, body surface area or age and in very young or very sick children inability to swallow and palatability issues are observed. Effectiveness and safety of treatment are also affected by the dependence on carers and knowledge of use of the medicine by both the carer and user.

Consequently, adult solid oral dosage forms are, in some cases, inappropriate and need to be modified prior to administration leading to various practices, such as

preparing extemporaneous formulations, crushing tablets, opening capsules and adding to food or drinks, giving oral anticonvulsants rectally, utilising intravenous formulations for oral use and using ophthalmic preparations in the ear (26, 27). Crushing a licensed tablet formulation or opening a capsule are the most common forms of manipulation used to prepare extemporaneous products. The resulting powder is either dissolved or suspended with various excipients to prepare an oral liquid formulation or redistributed in sachets or smaller capsules. Cutting a tablet into smaller segments in order to obtain the appropriate dose for the paediatric patient is also applied. The manipulated formulations are then mixed with food or drinks to facilitate administration and improve acceptability. Even though these formulations are relatively quick to prepare and can allow dosage flexibility, their physical, chemical and microbial stability and palatability are not guaranteed (3, 25). Insufficient data to support practice, expiration dating of compounded formulations, unknown bioavailability, and extemporaneous compounding errors are associated with this practice.

4. Age-related factors affecting adherence to paediatric medicines

Adherence to prescribed medication varies between 11 and 93 % amongst the paediatric population (median value of 58 %) and is lower than the one reported in adults (30-70 %) (28-30). Formulation acceptability facilitates adherence to medication in children and the achievement of intended treatment outcomes (5). Variability of acceptability of dosage form(s) in young patients relates to individual characteristics (age and individual health status, behaviour, disabilities and background), difficulties in medicines' administration (manipulation of medicines and taste), medication-taking behaviour (influence of family, school and life situation/context), and culture (3, 5, 7).

a) Individual characteristics

A paediatric patient cannot be standardised. According to physical development and psychological understanding, the ability to use different dosage forms can vary greatly. The age at which children can safely swallow solid oral dosage forms depends on health status and inter-patient differences (5).

b) Disease status

The type of disease, acute or chronic, as well as the duration of treatment and the required number of medicines affect acceptability of medicines. Paediatric patients who are acutely unwell may be frightened and less co-operative than usual, especially if in pain or with fever. Sometimes medications have to be administered during school hours and training of the carer is required. Paediatric patients with long-term illness requiring continuing medication can be trained to take solid dosage forms from a relatively early age of 3-5 years, whereas for younger children training is given to carers (7, 9).

c) Carers

Dependence on a carer is common for the majority of the paediatric age groups with the exception of adolescents. The willingness and ability of the carer influence the acceptability of the medicine and treatment outcome (4). Attention should be given to the ease of administration by the carer as it influences dosage form choice and adherence (3). Moreover, carers may follow different administration techniques in the domiciliary/pragmatic environment than the ones recommended to them by healthcare professionals (31).

d) Adolescence and peer pressure

Information on handling medicinal products during puberty is scarce (7). Adolescents are usually responsible for their own medicine administration and capable of taking medication without mixing it with food or drinks. They may be rebellious though and reject medicinal products they have previously taken or be affected by peer pressure or recalcitrance. Lifestyle changes also may impose the need for discrete and portable dosage forms.

e) Cultural and geographical differences

The acceptability of medicines can be influenced by the location and/or setting in which the administration takes place. Interpretation of colour, form and taste of the medicine linked to strength and effect presents sociocultural variability. For example, a large pill can be interpreted as stronger than a small one or a bitter tasting medicine as more powerful than a sweet one. Traditional homeopathic or herbal medicines are preferred in some societies instead of western medicines that are

viewed as ‘too strong’ or with ‘too many’ side effects (32). Traditional beliefs, misconceptions and irrational use of medicines, may be more pronounced in resource-poor settings (education) and where other services are limited (*i.e*. access to clean water). The preferred method for dispensing extemporaneous preparations relates to the country; for example, in the UK, Ireland and Norway oral liquids tend to be prepared, whereas in France and Spain capsules are usually chosen, and in Italy powders are preferred (25). Differences in the palatability and acceptability of different routes of administration in different countries and different religions are well recognised, even though data for evaluation of the effect of global sociocultural differences on adherence to paediatric medicines is limited (32).

f) Palatability

Children have a low tolerance for disagreeable taste, smell and texture which affects their adherence to oral formulations. Size, taste and texture have been found to be the most significant factors controlling the drug administration to children (8, 9). To overcome poor taste, and to improve acceptability to paediatric patients, a wide range of drugs are mixed with food prior to administration (9).

5. Improving palatability and acceptability: mixing medication with food or drinks

5.1 Current practice and legislation

Mixing medication with food or drinks intends to mask the unsatisfactory palatability of a formulation, in cases that it cannot be further improved through dosage form design, and to enhance acceptability through swallowing facilitation or texture improvement. Children often struggle with dysphagia either because the tablet or capsule is ‘too large’ to swallow or the liquid is ‘too bitter’ or ‘unpleasant’. Therefore, carers mix the medication (usually after manipulation of the initial dosage form) with a drink (*i.e.* fruit juice) or with food (*i.e.* yoghurt or applesauce) (7-9, 33). This is particularly prevalent in children with neurological impairments and mental health difficulties, as the majority of psychoactive medicines are unlicensed in children and have a bitter taste (8). In a recent study, conducted in a large paediatric population suffering from different chronic conditions, manipulation of the

formulations in the domiciliary environment reported by almost one third (74/252) of respondents was mainly associated with the age of child, socioeconomic status, taste, texture, and volume/ or quantity of dosage form. 19 % (94/499) of formulations were manipulated with the majority of these (93 %, 87/94) to be manipulated 'always' (*i.e.* prior to every dose administration) (31).

Current legislation highlights that whatever the reason for mixing medicines with food or drinks is, the rationale should be discussed and justified, and relevant information should be included in the summary of product characteristics (SmPC) and patient information leaflet (PIL) (7). Clear instructions on the type of food and drinks appropriate for mixing with the paediatric medicine should be given. Appropriate warnings in cases when such practice is unsuitable or has not been studied must be provided. Any mixing outside the recommendations is responsibility of the health care professional or the user (3, 7). Instructions on the quantity of the food or drinks to be used and the acceptable time period after mixing based on the chemical stability of the drug should be noted. If chewing of the product is expected to alter product performance or influence acceptability it must be clearly stated.

Different food or drinks can have different effects on the paediatric medicine due to their properties, such as pH, osmolality and viscosity. For example, pudding and applesauce are both considered as a 'soft food', but they had a different effect on drug's absorption when mixed with the same drug (34). The possible effect of food or drinks on the biopharmaceutical characteristics of the medicinal product and on its acceptability, compatibility and stability should be studied. Assessment of the impact of food and drinks on drug's bioavailability may be extrapolated from studies in adults, if relevant to the paediatric medicine; for example, adult food effect studies and achlorhydria studies.

5.2 Current platforms

National and/or regional formularies (quite often hospital formularies) are used for paediatric medicines, especially in cases where effective adult doses of newly approved medicines cannot be down-scaled based on a simplistic body weight extrapolation. In the UK, the British National Formulary for Children (BNF-C) was established in 2006 in order to compile available information and harmonize

practice. The BNF-C lists the correct mode of administration of paediatric medicines, with recommendations for mixing the drugs with food or drinks, when applicable. In practice, several Hospital Formularies are used with recommendations for mixing paediatric medicines with food or drinks, some of which are not recorded in the BNF-C.

For the purpose of this review, both the BNF-C (26) and the Guy's and St. Thomas, King's College and University Lewisham Hospitals' Paediatric Formulary (35) were consulted, in order to access the drugs recommended to be mixed with food and/or drinks prior to oral administration, and compare differences between these formularies (Table 1.2). 61 drugs are recommended to be mixed with food or drinks prior to administration. Differences in the instructions between the two sources are observed and only 30 drugs are included in both formularies although sometimes with different recommendations; for example, Sodium Phenylbutyrate is recommended to be mixed with meals or milk in the Hospital Formulary but not in the BNF-C. A more concerning issue arises in the case of Tenofovir Disoproxil, as the BNF-C warns against mixing with liquids whereas in the Hospital Formulary mixing of the granules with orange juice or water is advised. The BCS Class of the drug was added (information not included in the Formularies). The paediatric age subgroups were classified as Neonates, Infants, Children and Adolescents (Table 1.1). Seven formulation types were identified: tablets crushed prior to mixing, opened capsules whose contents are sprinkled on or mixed with the food or drink, ampoules for IV administration which are recommended to be diluted and administered orally, granules, powder, solutions and suspensions. The type of food or drinks recommended were categorized in 'Soft foods', 'Meals', 'Juice', 'Milk', 'Water' and 'Others'. 'Soft foods' include yoghurt, applesauce, jam, honey and/or ice-cream; 'milk' refers to particular types as breast or skimmed milk; 'juices' are fruit, apple, orange, blackcurrant or squashes and 'others' refer to cola or tea. Specific vehicles recommended are included in the 'Notes' column. Recommended administration in water was noted in the cases where water was an alternative vehicle to other drinks. Drugs for which it was noted that tablets 'may be crushed or dissolved' without specific suggestion for the vehicles are not included.

Table 1.2. Drugs recommended to be mixed with food (according to the BNF-C (A) and Guy's and St. Thomas, King's College and University Lewisham Hospitals' Paediatric Formulary (B))

Drug	BCS class	Age	Formulation type	Mixed with						Notes
				Soft foods	Meals	Juice	Milk	Water	Others	
Acetylcysteine (A) (B)	I (36)	N I C A	Granules; ampoule*			**X**			**X**	Juices: blackcurrant, orange Others: cola, orange or blackcurrant syrup
Betaine (A) (B)	-	N I C A	Powder	**X**	**X**	**X**	**X**	**X**		Meals: formula, (+)
Budesonide (A)	II (37)	A	Capsule			**X**				Juices: apple, orange
Calcium carbonate (A)(B)	-	N	Tablet; solution		**X**			**X**		- (should be mixed thoroughly to avoid precipitation)
Calcium Polysterene Sulfonate (A) (B)	-	I C A	Powder				**X**	**X**	**X**	Others: soft drinks (should not be given with squash or fruit juice)
Carnitine (l-carnitine) (B)	-	N I C A	Solution			**X**		**X**		Juices: fruit
Charcoal, activated (A)	-	N I C A	Suspension; capsule; tablet			**X**			**X**	Juices: fruit Others: soft drinks (*e.g.* caffeine-free diet cola)
Chloral hydrate (A)	-	N I C A	Solution; tablet				**X**	**X**		-
Cholestyramine (A) (B)	-	I C A	Powder	**X**		**X**	**X**	**X**	**X**	Soft foods: pulpy fruits, thin soups Juices: fruit Milk: skimmed Others: liquids
Clindamycin (B)	I (38)	N I C A	Capsule	**X**	**X**	**X**		**X**		-

Drug	BCS class	Age	Formulation type	Mixed with						Notes
				Soft foods	Meals	Juice	Milk	Water	Others	
Colecalciferol (A)	-	I C A	Solution	**X**	**X**		**X**			Soft foods, meals: cold or lukewarm
Colestipol hydrochloride (A)(B)	-	A	Granules	**X**		**X**	**X**	**X**	**X**	Soft foods: thin soups, pulpy fruits, yoghurt Juices: fruit Milk: skimmed Others: cereals
Cyclophosphamide (B)	I (38)	**	Ampoule*			**X**				Juices: fruit
Cyclosporine (A) (B)	II (39)	I C A	Solution			**X**				Juices: orange, apple, squash (should not be mixed with blackcurrant juice)
Deferasirox (A) (B)	II (40)	I C A	Dispersible tablet			**X**		**X**		Juices: apple, orange
Didanosine (A)	III (38)	I C A	Chewable tablet			**X**		**X**		Juices: apple
Docusate sodium (A) (B)	-	I C A	Solution			**X**	**X**			Juices: squash Milk: breast milk, (+)
Efavirenz (B)	II (41)	C A	Capsule	**X**	**X**					-
Enoximone (B)	-	N I C A	Ampoule*		**X**		**X**			Meals: formula
Fosamprenavir (B)	II (42)	C A	Suspension	**X**	**X**					-
Gabapentin (B)	III (43)	C A	Capsule			**X**			**X**	Juices: blackcurrant Others: strong tasting liquid
Gaviscon (B)	-	N I C A	Powder		**X**		**X**	**X**		(should not be mixed with feed thickeners)
Hydromorphone hydrochloride (A)	-	A	Capsule (IR or MR)	**X**						-

Drug	BCS class	Age	Formulation type	Mixed with						Notes
				Soft foods	Meals	Juice	Milk	Water	Others	
Imatinib (A)	II† (44)	I C A	Tablet			**X**		**X**		Juices: apple
Iodine (A) (B)	-	N I C A	Solution				**X**	**X**		-
Labetalol hydrochloride (A)(B)	-	N I C A	Ampoule*			**X**				Juices: squash
Lactulose (A)(B)	II (45)	I C A	Solution; powder		**X**	**X**		**X**		Juices: fruit (Mix with food/drinks to reduce nausea)
Lisdexamfetamine mesilate (A)	-	C A	Capsule	**X**		**X**		**X**		Soft foods: yoghurt Juices: orange
Magnesium aspartate (A)	-	I C A	Powder; granules			**X**		**X**	**X**	Juices: orange Others: tea
Mefloquine (A)	II (46)	I C A	Tablet	**X**						Soft foods: honey, jam, (+)
Megalumine amidotrizoate with sodium amidotrizoate (A)	-	I C A	Solution			**X**		**X**		Juices: fruit
Mercaptamine (A) (B)	-	N I C A	Capsule	**X**	**X**	**V**			**V**	Strongly flavoured drinks or food at a temperature suitable for eating (should avoid acidic drinks)
Mesalazine (A) (B)	IV (45)	C A	Granules			**X**		**X**		Juices: orange
Mesna (A)(B)	-	C	Ampoule*			**X**			**X**	Juices: orange, (+) Others: cola, (+)
Metformin (B)	III (47)	C A	Powder			**X**	**X**	**X**	**X**	Juices: orange Water: sparkling Others: cola

Drug	BCS class	Age	Formulation type	Mixed with						Notes
				Soft foods	Meals	Juice	Milk	Water	Others	
Methylphenidate hydrochloride (A)(B)	I (45)	C A	Capsule (MR)	**X**						Soft foods: applesauce
Midazolam (A)(B)	I (48)	I C A	Ampoule*			**X**			**X**	Juices: apple, blackcurrant Others: cola, chocolate sauce
Montelukast (A)(B)	II (49)	C A	Granules	**X**						Soft foods: cold or at room temperature (not liquid)
Morphine (A)	I (43)	N I C A	Capsule (MR)	**X**						-
Olanzapine (A)	I† (44)	A	(Oro)dispersible tablet			**X**	**X**	**X**	**X**	Juices: apple, orange Others: coffee
Omeprazole (A)	II (45)	N I C A	Tablet (GR); Capsule	**X**		**X**		**X**		Soft foods: yoghurt Juices: fruit
Pancreatin (A)(B)	-	N I C A	Granules (GR); Capsule	**X**	**X**	**X**	**X**		**X**	Soft foods: acidic, jam, (+) Meals: formula Juices: apple Others: acidic soft drinks
Potassium iodide (B)	I (38)	N I	Capsule			**X**	**X**			-
		C	Capsule	**X**						Soft foods: jam, yoghurt, honey, (+)
Proguanil hydrochloride (A)(B)	I (38)	N I C A	Tablet	**X**			**X**			Soft foods: jam, honey, (+)
Risperidone (A)(B)	II† (44)	C A	Solution			**X**	**X**	**X**	**X**	Juices: fruit, orange Water: mineral Others: coffee, tea
Ritonavir (A) (B)	IV (38)	C A	Solution	**X**			**X**			Soft foods: ice cream Milk: chocolate (should not be mixed with water)

Drug	BCS class	Age	Formulation type	Mixed with						Notes
				Soft foods	Meals	Juice	Milk	Water	Others	
Senna with ispaghula husk (A)	-	A	Granules			**X**	**X**	**X**	**X**	Other: liquids
Sertraline (B)	I† (44)	C	Tablet			**X**		**X**		Juices: orange, blackcurrant squash
Sirolimus (A)(B)	II (50)	I C A	Solution			**X**		**X**		Juices: orange (should not be mixed with other liquids)
Sodium benzoate (A)(B)	-	N I C	Solution; powder		**X**	**X**	**X**			Juices: fruit Milk: breast
Sodium chloride (A)	I (45)	N	Tablet (MR)		**X**		**X**			Meal: formula Milk: breast
Sodium phenylbutyrate (A)(B)	-	N I C A	Granules; tablet		**V**	**X**	**V**			Juices: fruit
Sodium valproate (A)(B)	I (38)	N I C A	Granules (MR); capsule (MR)	**X**		**X**	**X**	**X**	**X**	Soft foods: cold Others: cold soft drinks
Stavudine (B)	I (38, 51)	N I C A	Capsule	**X**	**X**					-
Sterculia (A)	-	C A	Granules; tablet	**X**						Soft foods: yoghurt, (+)
Sucralfate (B)	-	N I C A	Solution; tablet	**X**	**X**			**X**		-
Tenofovir disoproxil (A)(B)	III† (44)	C A	Granules	**X**		**V**		**V**		Soft foods: yoghurt, applesauce, (+) Juices: orange (should not be mixed with liquids (A))
Theophylline (A)(B)	I (52)	C A	Capsule	**X**						Soft foods: yoghurt, (+)
Topiramate (A)(B)	III (43)	C A	Capsule	**X**						
			Tablet (B)		**V**	**V**		**V**	**V**	

Drug	BCS class	Age	Formulation type	Mixed with						Notes
				Soft foods	Meals	Juice	Milk	Water	Others	
Vigabatrin (A)(B)	I (53)	C A	Powder; tablet	**X**		**X**	**X**	**X**	**X**	Juices: fruit, squash Others: soft drinks
Vitamins with minerals and trace elements (A)	-	C	Emulsion			**X**	**X**		**X**	Juices: fruit Others: cereals

(A) BNF-C
(B) Paediatric formulary
N Neonates
I Infants
C Children

A adolescents
* solution for injection
GR Gastro-resistant
MR Modified-release
IR Immediate release

V recommendations from (B) but not (A)
(+) others
† Predictive values
** Unlicensed medicine (no age is specified)

5.3 Biopharmaceutical properties of drugs and mixing with food and drinks

The biopharmaceutical characteristics of the medicinal product will be affected by its mixing with food or drinks. Analyses were performed to reveal potential correlations of the biopharmaceutical properties of the drugs with the age group, the type of formulation administered, and the type of food and drinks used for the mixing with the drug.

The Biopharmaceutics Classification System (BCS) established by Amidon et al. (1995), which categorises drugs based on their solubility and permeability, is a regulatory framework for oral drug products for adults (54). Out of the 61 drugs listed (Table 2.2), 44% could not been assigned to a BCS class based on the published information regarding their solubility and permeability (and were denoted as 'BCS unclassified'), 25% belong to BCS class 1, 20% to BCS class 2, 8% to BCS class 3 and 3% to BCS class 4 (Figure 1.1). It is worth noting that the majority of drugs suggested to be co-administered with food and drinks are drugs with high permeability.

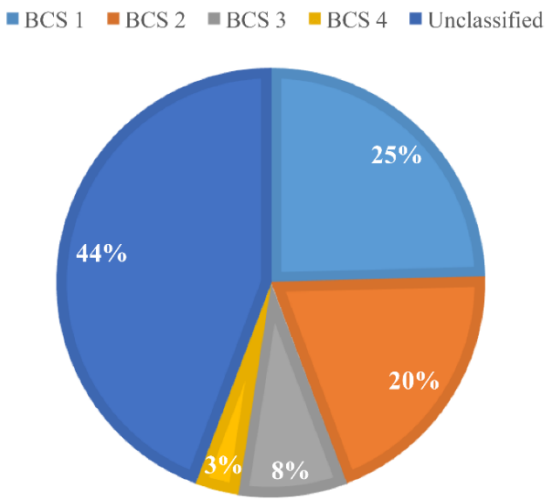


Figure 1.1. BCS classification of the drugs recommended to be mixed with food and/or drinks

a) BCS class of the drug vs age group

The relationship between the paediatric age group and the BCS class of the drug is presented in Figure 1.2. The majority of drugs recommended to be given with food

or drinks to neonates are BCS class 1 drugs. From the drugs identified from the two formularies studied, there are no drugs belonging to BCS class 3 or 4 suggested to be mixed with foods or drinks to neonates. For infants, drugs recommended to be mixed with food or drinks are drugs belonging to all BCS classes with the exception of BCS class 4 drugs. Regarding the other two subpopulations (children and adolescents), from the analysis performed, it can be observed that drugs from all four BCS classes are indicated to be mixed with foods or drinks (Figure 1.2).

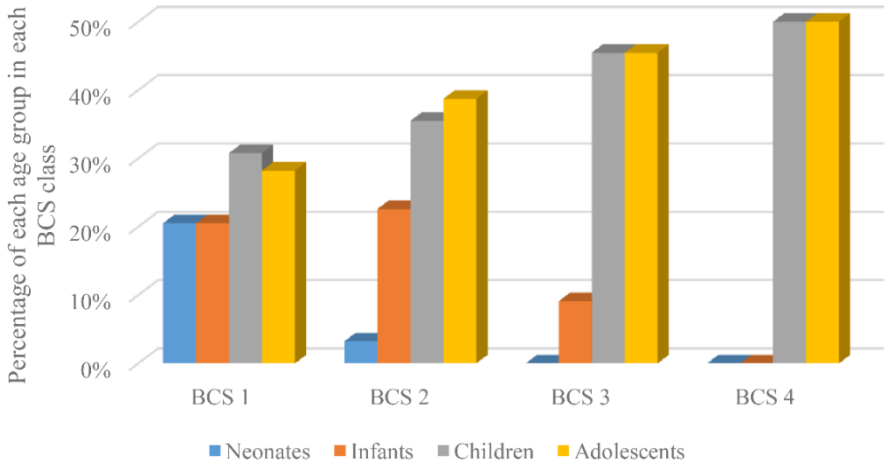


Figure 1.2. Percentage of drugs of each BCS class in relation to the paediatric age group

b) BCS class of the drug vs type of formulation

In Figure 1.3, the relationship between the drug's BCS class and the type of formulation administered and mixed with food or drinks is shown. Capsules and tablets are the most common formulations used in this practice for BCS class 1 and BCS class 3 drugs and solutions, capsules and tablets for BCS Class 2 drugs. BCS class 4 compounds formulated as granules and solutions are the prevalent dosage forms mixed with foods or drinks.

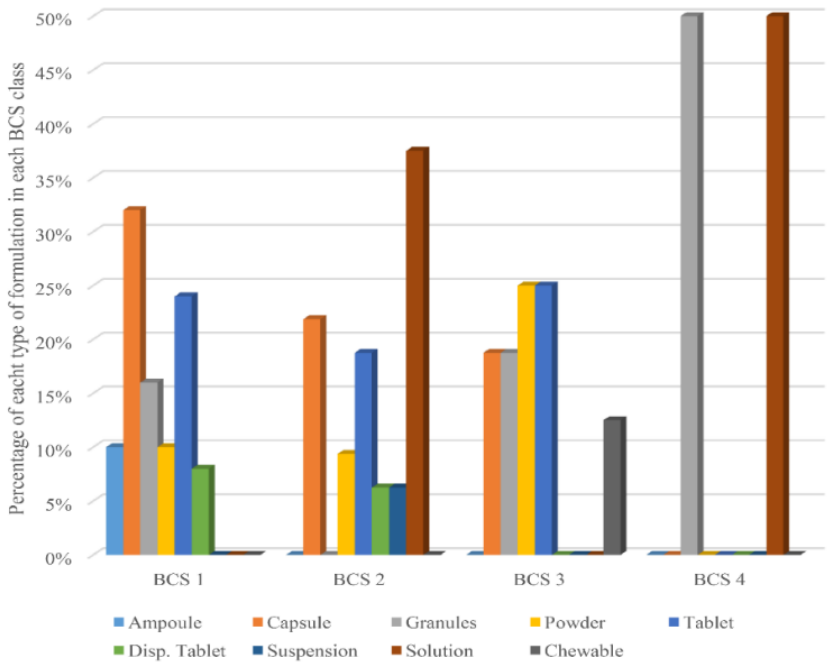


Figure 1.3. Percentage of the formulation type in relation to the BCS class of the drugs

c) BCS class of the drug vs type of food

As illustrated in Figure 1.4, juice is the most prevalent type of vehicle used for drugs belonging to all the BCS classes. Soft foods are commonly recommended for mixing with BCS class 1 and 2 drugs, milk with BCS class 4 drugs, whereas meals are the less commonly suggested vehicles to be mixed with paediatric medicines. The characteristics of the vehicles may have an impact on drug's stability and solubility compromising its bioavailability and therapeutic outcomes. For example, most fruit juices and cola due to their low acidic pH can affect the stability of certain API's. Mixing soft foods such as ice cream, with BCS class 2 drugs (lipophilic drugs) could have an effect on drug's solubility due to partitioning into the lipophilic phase. Variability on the outcome would be expected when drugs are mixed with different food or drinks belonging in the same food or drink 'type' due to the intra-variability of the characteristics of vehicles of the same food or drink 'type'.

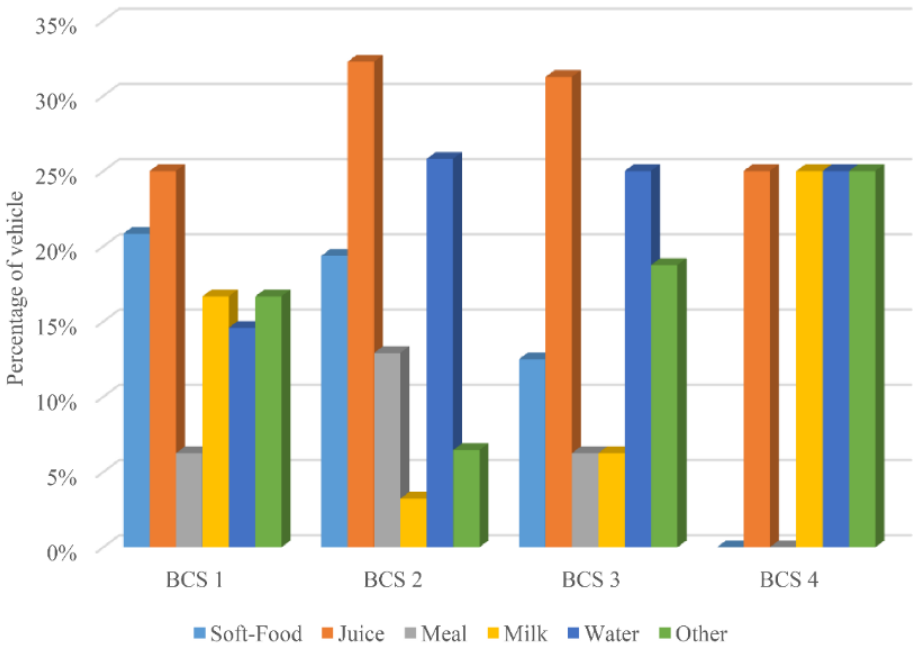


Figure 1.4. Percentage of the vehicle type in relation to the BCS class of the drugs

d) Type of food vs type of formulation

The relationship between the type of vehicle and the type of formulation is presented in Figure 1.5. Ampoules are recommended to be mixed either with juice or other types of drinks (tea or cola). When this practise is followed, the risk of precipitation due to dilution or pH of the liquid vehicle should be considered. Even though paediatric patients do not typically drink hot liquids, the effect of temperature when preparing a formula or tea on the stability of the drug should be studied. Soft foods or meals are suggested for the mixing with suspensions, and soft foods and juice for capsules and granules. All vehicles with the exception of soft foods are reported for the mixing with solutions, whereas tablets and dispersible tablets, are recommended to be mixed with all the vehicles, without preference. Based on the drug's and vehicle's characteristics' the potential impact of the mixing practise on drug's solubility and dissolution and subsequently on drug's absorption should be explored. Viscosity, fat and dairy-protein content are other characteristics which apart from their effect on gastric emptying rate, may also interfere with the drug's behaviour and alter its bioavailability.

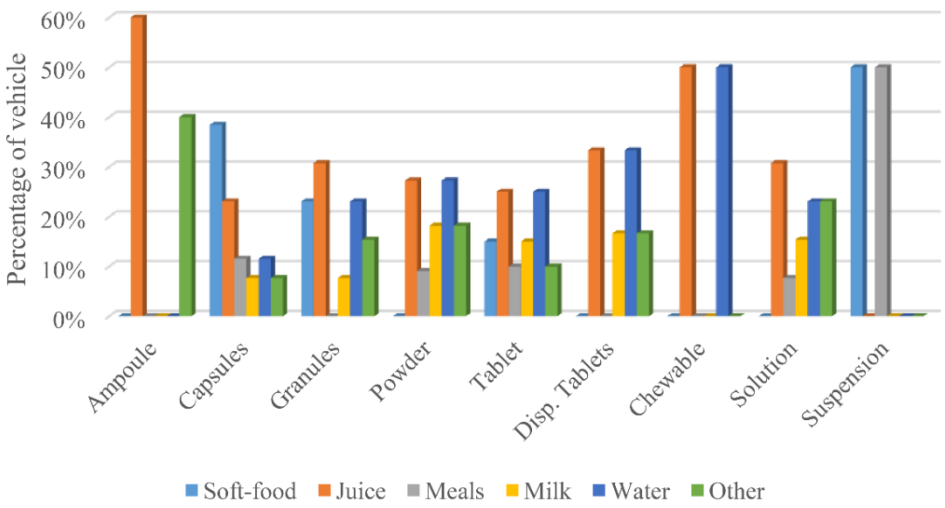


Figure 1.5. Percentage of the vehicle type in relation to the formulation

e) Type of formulation vs age group

The relationship between the formulation type and the age group is shown in Figure 1.6. For neonates, from the seven types of formulations identified in in this study, only ampoules, capsule contents and suspensions are recommended to be mixed with food and drinks. For all the other groups, all the formulation types are accepted.

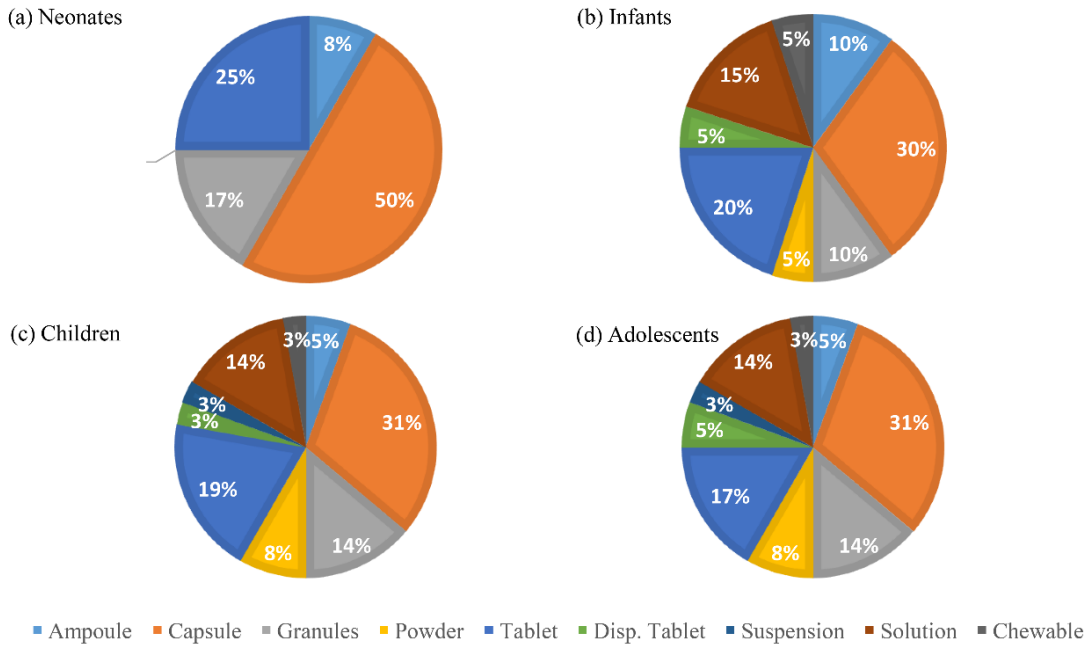


Figure 1.6. Percentage of formulation type in relation to the paediatric age subgroup

6. Administration techniques reported by healthcare professionals and parents/carers

Mixing medication with food and/or drinks is a common practice on paediatric wards with nurses being usually responsible for administering medication (8, 9). In a recent study, it was found that the majority of paediatric nurses modify oral dosage forms or mix medication with food or drinks prior to administration (8). The most common food/drinks reported to be used were fruit yoghurts, crushed bananas, and diluted and concentrated fruit juices. Co-mixing was perceived as a time-consuming process and preference was expressed for mixing the powdered dosage form(s) into juice or a liquid rather than into solid foods. The actual method used to mix the medication with the food/ drinks was not consistent, with some interviewees reporting that they 'poured the contents of the capsule/crushed tablet onto a spoon and added the food item to it', whilst others reported that they 'dispersed the powdered medicine directly into the food' (8). In a survey performed in a hospital in Cape Town (South Africa) to investigate carers' practices and perceptions regarding tuberculosis (TB) treatment of children, about two thirds of the interviewees reported that TB medication was given after meals (33). The medication was crushed, dissolved and/or mixed with food or drinks in over half of the cases, while 30 % reported that medication was swallowed or chewed. It should be noted though that among the drug formulations commonly used for TB, only one brand of tablets can be chewed or dispersed in 5 mL of water. All other tablets are not dispersible, and for one of the tablet formulations crushing has been associated with treatment failure due to reduced bioavailability of the drug (33, 55). Moreover, parts of crushed or dissolved tablets or contents of capsules may not be swallowed, resulting in administration of a lower dose than the intended one.

In another study, the ad hoc techniques that parents and carers had reported to healthcare professional groups, as well as the techniques that the healthcare professionals recommended to them for the paediatric medicine administration were reviewed (9). Nurses gave examples of what is actually done in the wards with yoghurt being the vehicle of preference, whereas medical practitioners described in detail the practice that the parents follow which does not always correspond to the practice on the wards. The majority of nurses were unaware of the potential drug stability and degradation issues when performing ad hoc administration techniques.

Some of them were not conscious of the possible impact upon clinical outcome, with one nurse even saying "just try whatever the child likes". Pharmacists expressed their concern regarding the impact of these techniques on drug's pharmacokinetics, for example the effect of acidic juice on drug's solubility and absorption. The participating healthcare professionals were unaware of the level of evidence supporting the various drug/ formulation manipulation techniques. The need for more information about drug-food compatibilities were revealed and training issues were identified, as few nurses were aware of the pharmaceutical implications of this practice.

Parents/carers may not always follow the administration techniques recommended to them by healthcare professionals in the domiciliary environment, and it is not clear if healthcare professionals are always aware of these practices (31).

7. Effect of mixing medicines with food and drinks on drug's bioavailability

Combination of medication with food or drinks to mask the taste of the drug, can have an effect on drug's safety and efficacy. Even though potential treatment issues related to the crushing of modified release tablets or capsules are well recognised and understood, this doesn't seem to apply for issues associated with the crushing of other formulation types (for example immediate release formulations) (56, 57). Increased bioavailability or sub-therapeutic drug levels due to loss of the dose during crushing and transfer of immediate release tablets have been observed (55, 58-60). Crushing of tablets or opening of capsules with enteric coating could result in decreased drug absorption and efficacy or in irritation on gastrointestinal mucosa depending on the drug formulated (18). Drug loss through the crushing process is also a concern as children may receive reduced and variable dosing. Contamination issues may occur if a previously uncleaned vessel is used for the paediatric medicine administration. Assessment of drug pharmacokinetics in children with crushed tablets is performed under a 'standardised' method, *i.e.* using water for dissolving the drug and may not represent accurate, realistic daily preparation practices. Delivering medications with fruit juices such as grapefruit, orange or apple juice affects absorption of several drugs possibly due to their acidic pH and increased

potential for drug precipitation or degradation (61, 62). Alterations of physiological conditions such as gastric emptying, and of gastrointestinal contents' properties such as viscosity, osmolality and calorific content after food administration can affect drug's pharmacokinetics (63, 64). In some cases, crushing tablets or opening capsules and mixing with a small volume of soft foods did not alter bioavailability significantly (17, 65). In other cases though, absorption was impaired when crushed tablets were mixed with pudding compared to the use of applesauce (34) and absorption was delayed after mixing enteric-coated beads with yoghurt or applesauce (66). Comparative release and dissolution studies of four drugs from crushed and whole tablets in six different foods and drinks frequently used in the clinical setting revealed that the impact on drug's dissolution depends on the drug properties and the vehicle properties (18). Furthermore, stability issues can arise when/if there is a delay between preparation and administration.

Food–drug interaction studies are widely reported in adult populations, with dedicated regulatory guidance on the conduct of food effect clinical studies (67, 68). For paediatric populations the guidance surrounding food effect is limited (17). In the USA, the "Pediatric Study Decision Tree" (67) allows extrapolation from adult data sets if there is sufficient similarity of both the disease progression and the response to intervention between source and target population. If the exposure-response relationship of the medicinal product is similar, the only PK studies required in paediatric populations are those for dose determination and safety evaluation. Similarly in the EU, EMA guidance states that relative bioavailability comparisons of paediatric formulations with the adult oral formulations should typically be conducted in adults with only dose selection PK studies required in paediatric populations (7, 69). Therefore, the majority of paediatric pharmacokinetic studies are conducted in the fasted state with very limited pharmacokinetic studies in the fed state in which milk or standardised breakfasts are mainly used (17).

The extrapolation of food effects observed in adults into paediatric populations is an unexplored and complex area as there are key differences between both populations, namely:

- Biological and anatomical differences in the gastrointestinal tract;

- Different feeding patterns, both in terms of food composition and feeding frequency;
- Reduced volume ingested by younger patients that affects the gastric emptying rate and differences to the emptying rate observed in adult studies are expected.

The nature of the food utilised in common practice by carers in paediatric patients adds complexity to the extrapolation of the food effect from adult studies (33). Food effect can be different between paediatric and adult studies (17); for example, food effect was more marked in children compared to adults for sustained-release theophylline formulations with bioavailability in the fed state being lower in children than in adults (34).

8. Conclusions

A global effort to improve paediatric accessibility to medicines is observed, which in turn has increased the number of drugs tested in and labelled for use in children (1). Healthcare professionals, parents or carers face the need to manipulate an adult medicine and mix it with food and/or drinks prior to administration in order to improve palatability. Although there is some information available regarding drug manipulation and the subsequent effect on drug stability/degradation, until recently this information had limited relevance as it mainly considered administration via PEG (percutaneous endoscopic gastrostomy) tubes and not mixing with food (70). Points to consider would relate to the type of food used in the study in terms of acceptance from the paediatric population and its uniform composition in different countries. For example, studies have been performed with applesauce which is not very well accepted amongst the paediatric population and may differ in sugar content in different countries (71). Furthermore, viscosity of the vehicle affects dissolution and release aspects from crushed tablets (18). The pH of the vehicle affects drug's stability. For example, the pH of fruit yoghurts that are commonly used vehicles could compromise the chemical stability of drugs that are acid sensitive, particularly in the case of manipulation of enteric-coated dosage forms (8, 9, 72).

The European Committee on Pharmaceuticals and Pharmaceutical Care (CD-P-PH) and the European Directorate for the Quality of Medicines & HealthCare (EDQM) have recently launched an initiative to make a European Paediatric Formulary (73). This Formulary will give easy access to hospital and retail pharmacies across Europe to monographs for the preparation of extemporaneous formulations for paediatric medicines, and the practice amongst all countries and regions can be harmonized. The inevitable use of deduction as a means to obtain what is 'probably' the best therapy for a child will gradually disappear, and the continuous production and availability of evidence-based information for health professionals and carers will lead to better therapeutic approaches (74).

References

1. Turner MA, Catapano M, Hirschfeld S, Giaquinto C, Global Research in P. Paediatric drug development: the impact of evolving regulations. Adv Drug Deliv Rev. 2014;73:2-13.

2. Ernest TB, Elder DP, Martini LG, Roberts M, Ford JL. Developing paediatric medicines: identifying the needs and recognizing the challenges. J Pharm Pharmacol. 2007;59(8):1043-55.

3. World Health Organization. Development of paediatric medicines: points to consider in pharmaceutical development (Working document QAS/08.257/Rev.3). 2011. http://www.who.int/medicines/areas/quality_safety/quality_assurance/Rev3-PaediatricMedicinesDevelopment_QAS08-257Rev3_17082011.pdf. Accessed 21 January 2016.

4. Liu F, Ranmal S, Batchelor HK, Orlu-Gul M, Ernest TB, Thomas IW, et al. Formulation factors affecting acceptability of oral medicines in children. Int J Pharm. 2015;492(1-2):341-3.

5. Liu F, Ranmal S, Batchelor HK, Orlu-Gul M, Ernest TB, Thomas IW, et al. Patient-centred pharmaceutical design to improve acceptability of medicines: similarities and differences in paediatric and geriatric populations. Drugs. 2014;74(16):1871-89.

6. Lopez FL, Ernest TB, Tuleu C, Gul MO. Formulation approaches to pediatric oral drug delivery: benefits and limitations of current platforms. Expert Opin Drug Deliv. 2015;12(11):1727-40.

7. Committee for Medicinal Products for Human Use (CHMP) & Paediatric Committee (PDCO). Guideline on pharmaceutical development of medicines for paediatric use EMA/CHMP/QWP/805880/2012 Rev. 2. 2013. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/07/WC500147002.pdf. Accessed 27 January 2016.

8. Akram G, Mullen AB. Paediatric nurses' knowledge and practice of mixing medication into foodstuff. Int J Pharm Pract. 2012;20(3):191-8.

9. Venables R, Stirling H, Batchelor H, Marriott J. Problems with oral formulations prescribed to children: a focus group study of healthcare professionals. Int J Clin Pharm. 2015;37(6):1057-67.

10. European Medicines Agency. ICH Topic E 11 Clinical Investigation of Medicinal Products in the Paediatric Population. 2001. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002926.pdf. Accessed 20 January 2016

11. Food and Drug Administration. Providing information about pediatric uses of medical devices under section 515A of the Federal Food, Drug and Cosmetic Act. RockVille, MD; 2013.

12. World Health Organisation. Paediatric Age categories to be used in differentiation between listing on a Model Essential Medicines List for Children. 2007. http://archives.who.int/eml/expcom/children/Items/PositionPaperAgeGroups.pdf. Assessed 19 January 2016.

13. Ivanovska V, Rademaker CM, van Dijk L, Mantel-Teeuwisse AK. Pediatric drug formulations: a review of challenges and progress. Pediatrics. 2014;134(2):361-72.

14. Food and Drug Administration. Paediatric research equity act of 2007, Title IV. 2007. http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049870.pdf. Accessed 1 March 2016.

15. Food and Drug Administration. Paediatric Research Equity Act of 2007, Title V. 2007. http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049870.pdf. Accessed 1 March 2016.

16. European Comission. Better medicines for children from concept to reality: progress report on the paediatric regulation (EC) N°1901/2006. 2013. http://ec.europa.eu/health/files/paediatrics/2013_com443/paediatric_report-com(2013)443_en.pdf. Accessed 8 March 2016.

17. Batchelor H. Influence of Food on Paediatric Gastrointestinal Drug Absorption Following Oral Administration: A Review. Children. 2015;2(2):244-71.

18. Manrique YJ, Lee DJ, Islam F, Nissen LM, Cichero JA, Stokes JR, et al. Crushed tablets: does the administration of food vehicles and thickened fluids to aid medication swallowing alter drug release? J Pharm Pharm Sci. 2014;17(2):207-19.

19. Committee for Medicinal Products for Human Use. Reflection paper: formulations of choice for the paediatric population. 2006. https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-formulations-choice-paediatric-population_en.pdf. Accessed 6 March 2016.

20. McIntyre J, Conroy S, Avery A, Corns H, Choonara I. Unlicensed and off label prescribing of drugs in general practice. Arch Dis Child. 2000;83(6):498-501.

21. Turner S, Nunn AJ, Fielding K, Choonara I. Adverse drug reactions to unlicensed and off-label drugs on paediatric wards: a prospective study. Acta Paediatr. 1999;88(9):965-8.

22. Turner S, Gill A, Nunn T, Hewitt B, Choonara I. Use of" off-label" and unlicensed drugs in paediatric intensive care unit. Lancet. 1996;347(9000):549-50.

23. Conroy S, McIntyre J, Choonara I. Unlicensed and off label drug use in neonates. Arch Dis Child. 1999;80(2):F142-F5.

24. Choonara I. Unlicensed and off-label drug use in children: implications for safety. Expert opin drug saf. 2004;3(2):81-3.

25. Nunn AJ. Making medicines that children can take. Arch Dis Child. 2003(88):369-71.

26. BNF for Children (BNFC) 2015-2016: Royal Pharmaceutical Society of Great Britain, British Medical Association, Pharmaceutical Press; 2016.

27. Levine S, Cohen MR. Preventing medication errors in pediatric and neonatal patients. In: Levine S, editor. Medication Errors, 2nd edn. Washington DC: Institute for safe medication practices: American Pharmaceutical Association; 2007. p. 469-92.

28. Burkhart P, Dunbar-Jacob J. Adherence research in the pediatric and adolescent populations: A decade in review2002. 199-229 p.

29. Staples B, Bravender T. Drug compliance in adolescents. Pediatr Drugs. 2002;4(8):503-13.

30. Winnick S, Lucas DO, Hartman AL, Toll D. How do you improve compliance? Pediatrics. 2005;115(6):e718-24.

31. Venables R, Batchelor H, Hodson J, Stirling H, Marriott J. Determination of formulation factors that affect oral medicines acceptability in a domiciliary paediatric population. Int J Pharm. 2015;480(1-2):55-62.

32. Seyberth HW, Rane A, Winter S. Pediatric clinical pharmacology: Springer Science & Business Media; 2011.

33. Belard S, Isaacs W, Black F, Bateman L, Madolo L, Munro J, et al. Treatment of childhood tuberculosis: caregivers' practices and perceptions in Cape Town, South Africa. Paediatr Int Child Health. 2015;35(1):24-8.

34. Pedersen S. Effects of food on the absorption of theophylline in children. J Allergy Clin Immunol. 1986;78(4 Pt 2):704-9.

35. Guy's and St. Thomas', King's College and University Lewisham Hospitals: Paediatric Formulary. 9th ed. Tomlin S, Kirk E, editors: Guy's & St Thomas' NHS Foundation Trust; 2012.

36. Zambon Nederland BV. Public assessment report of the Medicines Evaluation Board in the Netherlands: Fluimucil 600 mg tablets. 2014. http://db.cbg-meb.nl/Pars/h109369.pdf. Assessed 20 February 2016.

37. Bhatt H, Naik B, Dharamsi A. Solubility Enhancement of Budesonide and Statistical Optimization of Coating Variables for Targeted Drug Delivery. J Pharm (Cairo). 2014;2014:262194.

38. World Health Organisation. Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms (Annex 8) - WHO Technical Report Series, No. 937. 2006. http://apps.who.int/prequal/info_general/documents/TRS937/WHO_TRS_937__annex8_eng.pdf. Accessed 2 March 2016.

39. Yang SG. Biowaiver extension potential and IVIVC for BCS Class II drugs by formulation design: Case study for cyclosporine self-microemulsifying formulation. Arch Pharm Res. 2010;33(11):1835-42.

40. Al Durdunji A, AlKhatib HS, Al-Ghazawi M. Development of a biphasic dissolution test for Deferasirox dispersible tablets and its application in establishing an in vitro–in vivo correlation. Eur J Pharm Biopharm. 2016;102:9-18.

41. Panikumar A, Venkat R, Sunitha G, Sathesh B, Subrahmanyam C. Development of biorelevant and discriminating method for dissolution of efavirenz and its formulations. Asian J Pharm Clin Res. 2012;5(3):220-3.

42. Bergman E, Matsson EM, Hedeland M, Bondesson U, Knutson L, Lennernäs H. Effect of a single gemfibrozil dose on the pharmacokinetics of rosuvastatin in bile and plasma in healthy volunteers. J Clin Pharmacol. 2010;50(9):1039-49.

43. Takagi T, Ramachandran C, Bermejo M, Yamashita S, Yu LX, Amidon GL. A provisional biopharmaceutical classification of the top 200 oral drug products in the United States, Great Britain, Spain, and Japan. Mol pharm. 2006;3(6):631-43.

44. Drug Delivery Foundation. BCS database. 2015. http://www.tsrlinc.net/search.cfm. Assessed 10 March 2016.

45. Intra-Agency Agreement Between the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the U.S. Food and Drug Administration (FDA) Oral Formulations Platform—Report 1. 2011. http://bpca.nichd.nih.gov/collaborativeefforts/initiatives/upload/Formulations_Table_for_Web_11-02-11.pdf. Accessed 20 February 2016.

46. Cheng H, DeFulvio B, Kardos P, Wright J, Weinstein KE, Murray LJ, et al. In Vitro Permeability and Solubility Study of Mefloquine Hydrochloride According to the Biopharmaceutics Classification System (BCS) Guidelines. Absorption Systems, Exton, Pennsylvania, USA.

47. Lindenberg M, Kopp S, Dressman JB. Classification of orally administered drugs on the World Health Organization Model list of Essential Medicines according to the biopharmaceutics classification system. Eur J Pharm Biopharm. 2004;58(2):265-78.

48. Wu CY, Benet LZ. Predicting drug disposition via application of BCS: transport/absorption/elimination interplay and development of a biopharmaceutics drug disposition classification system. Pharm Res. 2005;22(1):11-23.

49. Okumu A, DiMaso M, Löbenberg R. Dynamic dissolution testing to establish in vitro/in vivo correlations for montelukast sodium, a poorly soluble drug. Pharm Res. 2008;25(12):2778-85.

50. Petruševska M, Homar M, Petek Bt, Resman A, Kocjan D, Urleb U, et al. Hydroxypropyl methylcellulose mediated precipitation inhibition of sirolimus: From a screening campaign to a proof-of-concept human study. Mol Pharm. 2013;10(6):2299-310.

51. Dezani AB, Pereira TM, Caffaro AM, Reis JM, Serra CHdR. Equilibrium solubility versus intrinsic dissolution: characterization of lamivudine, stavudine and zidovudine for BCS classification. Brazilian J Pharm Sci. 2013;49(4):853-63.

52. Brouwers J, Ingels F, Tack J, Augustijns P. Determination of intraluminal theophylline concentrations after oral intake of an immediate-and a slow-release dosage form. J Pharm Pharmacol. 2005;57(8):987-95.

53. Food and Drug Administration. Clinical Pharmacology Review: Sabril® (Vigabatrin). 2013. http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM374644.pdf. Accessed 29 February 2016.

54. Amidon GL, Lennernäs H, Shah VP, Crison JR. A Theoretical Basis for a Biopharmaceutic Drug Classification: The Correlation of in Vitro Drug Product Dissolution and in Vivo Bioavailability. Pharm res. 1995;12(3):413-20.

55. Best BM, Capparelli EV, Diep H, Rossi SS, Farrell MJ, Williams E, et al. Pharmacokinetics of lopinavir/ritonavir crushed versus whole tablets in children. J Acquir Immune Defic Syndr. 2011;58(4):385-91.

56. Nguyen TMU, Lau ET, Steadman KJ, Cichero JA, Dingle K, Nissen L. Pharmacist, general practitioner, and nurse perceptions, experiences, and knowledge of medication dosage form modification. Integr Pharm Res Pract. 2014;3:1-9.

57. Lippert C, Gbenado S, Qiu C, Lavin B, Kovacs SJ. The bioequivalence of telithromycin administered orally as crushed tablets versus tablets swallowed whole. J Clin Pharmacol. 2005;45(9):1025-31.

58. Zafar MU, Farkouh ME, Fuster V, Chesebro JH. Crushed clopidogrel administered via nasogastric tube has faster and greater absorption than oral whole tablets. J Interv Cardiol. 2009;22(4):385-9.

59. Henney HR, Fitzpatrick A, Stewart J, Runyan JD. Relative bioavailability of tizanidine hydrochloride capsule formulation compared with capsule contents administered in applesauce: A single-dose, open-label, randomized, two-way, crossover study in fasted healthy adult subjects. Clin ther. 2008;30(12):2263-71.

60. Paradiso LM, Roughead E, Gilbert A, Cosh D, Nation R, Barnes L, et al. Crushing or altering medications: what's happening in residential aged-care facilities? Austr J Ageing. 2002;21(3):123-7.

61. Lilja J, Raaska K, Neuvonen P. Effects of orange juice on the pharmacokinetics of atenolol. Eur J Clin Pharmacol. 2005;61(5-6):337-40.

62. Bailey DG. Fruit juice inhibition of uptake transport: a new type of food–drug interaction. Br J Clin Pharmacol. 2010;70(5):645-55.

63. Bowles A, Keane J, Ernest T, Clapham D, Tuleu C. Specific aspects of gastro-intestinal transit in children for drug delivery design. Int J Pharm. 2010;395(1-2):37-43.

64. Damle BD, Yan JH, Behr D, O'Mara E, Nichola P, Kaul S, et al. Effect of Food on the Oral Bioavailability of Didanosine from Encapsulated Enteric-Coated Beads. J Clin Pharmacol. 2002;42(4):419-27.

65. Gidal BE, Maly MM, Kowalski JW, Rutecki PA, Pitterle ME, Cook DE. Gabapentin absorption: effect of mixing with foods of varying macronutrient composition. Ann Pharmacother. 1998;32(4):405-9.

66. Shyu WC, Knupp CA, Pittman KA, Dunkle L, Barbhaiya RH. Food-induced reduction in bioavailability of didanosine. Clin Pharmacol Ther. 1991;50(5 Pt 1):503-7.

67. Food and Drug Administration. Guidance for Industry: Exposure-response relationship- study design, data analysis, and regulatory applications. 2003. https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072109.pdf. Assessed 15 March 2016.

68. European Medicines Agency: Guidance on clinical investigation of medicinal products in the paediatric population (CHMP/ICH/2711/99). 2000. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002926.pdf. Accessed on 10 February 2016.

69. Batchelor HK, Fotaki N, Klein S. Paediatric oral biopharmaceutics: key considerations and current challenges. Adv Drug Deliv Rev. 2014;73:102-26.

70. Phillips NM, Nay R. A systematic review of nursing administration of medication via enteral tubes in adults. J Clin Nurs. 2008;17(17):2257-65.

71. Wells KA, Losin WG. In vitro stability, potency, and dissolution of duloxetine enteric-coated pellets after exposure to applesauce, apple juice, and chocolate pudding. Clin Ther. 2008;30(7):1300-8.

72. Stubbs J, Haw C, Dickens G. Dose form modification - a common but potentially hazardous practice. A literature review and study of medication administration to older psychiatric inpatients. Int Psychogeriatr. 2008;20(3):616-27.

73. European Directorate for the quality of medicines and healthcare: A European Formulary for paediatric medicines - Rules and Criteria approved. 2016. https://www.edqm.eu/sites/default/files/press_release_european_paediatric_formulary_january_2016.pdf. Accessed 26 January 2016 [press release].

74. Bonati M, Pandolfini C. Is it time for a European formulary of paediatric medicines? Arch Dis Child. 2004;89(9):890-1.

Statement of Authorship and Letter of Copyright Permission

Statement of Authorship

This declaration concerns the article entitled:			
Recommended strategies for the oral administration of paediatric medicines with food and drinks in the context of their biopharmaceutical properties: a review.			
Publication status **Draft manuscript** [ ] **Submitted** [ ] **In review** [ ] **Accepted** [ ] **Published** [X]			
Publication details (reference)	Martir J, Flanagan T, Mann J, and Fotaki N. "Recommended strategies for the oral administration of paediatric medicines with food and drinks in the context of their biopharmaceutical properties: a review." Journal of Pharmacy and Pharmacology 69, no. 4 (2017): 384-397. doi:10.1111/jphp.12635 (https://onlinelibrary.wiley.com/doi/abs/10.1111/jphp.12635)		
Copyright status I hold the copyright for this material [ ] Copyright is retained by the publisher, but I have been given permission to replicate the material here [X]			
Candidate's contribution to the paper (detailed, and also given as percentage)	The candidate considerably contributed in: **Formulation of ideas:** The idea for the review paper was formulated by the academic supervisor, Dr. Fotaki (65 %), industrial supervisors, Dr. Flanagan and Dr. Mann (5 %), and the candidate (30 %). The initial idea for the content of the paper belongs to Dr. Fotaki. The candidate presented her proposals for the review paper content, which were reviewed and modified by Dr. Fotaki and the academic supervisors. **Design of methodology:** The methodology of the paper was designed by the academic supervisor, Dr. Fotaki (60 %), industrial supervisors (5 %), and the candidate (35 %). **Experimental work (literature review):** The literature review was carried out by the candidate (100 %). **Presentation of data in journal format:** Data was formatted and reviewed by the academic supervisor, Dr. Fotaki (55 %), industrial supervisors (15 %) and the candidate (30 %).		
Statement from Candidate	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature.		
Signed	Joana Filipa Louçã Martins	**Date**	08.04.2019

Letter of Copyright Permission

JOHN WILEY AND SONS LICENSE TERMS AND CONDITIONS

Apr 07, 2019

This Agreement between Joana Martir ("You") and John Wiley and Sons ("John Wiley and Sons") consists of your license details and the terms and conditions provided by John Wiley and Sons and Copyright Clearance Center.

License Number	4481910294509
License date	Dec 04, 2018
Licensed Content Publisher	John Wiley and Sons
Licensed Content Publication	Journal of Pharmacy and Pharamacology
Licensed Content Title	Recommended strategies for the oral administration of paediatric medicines with food and drinks in the context of their biopharmaceutical properties: a review
Licensed Content Author	Joana Martir, Talia Flanagan, James Mann, et al
Licensed Content Date	Oct 5, 2016
Licensed Content Volume	69
Licensed Content Issue	4
Licensed Content Pages	14
Type of use	Dissertation/Thesis
Requestor type	Author of this Wiley article
Format	Print and electronic
Portion	Full article
Will you be translating?	No
Title of your thesis / dissertation	Formulation performance in paediatric patients - in vivo predictive models and biowaivers
Expected completion date	Feb 2019
Expected size (number of pages)	190
Requestor Location	Joana Martir 1 The Academy 50-52 Wells Road Bath, BA23BB United Kingdom Attn: Joana Martir
Publisher Tax ID	EU826007151
Total	0.00 GBP

Chapter 2: Co-administration of paediatric medicines with food and drinks in the context of their physicochemical properties – a global perspective on practices and recommendations

Abstract

Objectives: The aims of this review were (i.) to describe the current recommended strategies for co-administration of paediatric medicines with food and drinks (vehicles); (ii.) to compare current administration recommendations from different countries; and (iii.) to obtain a global perspective on the rationale behind the choice of recommended vehicle, in the context of the physicochemical properties of the drug and formulation.

Methods: This study used a defined search strategy on the practices of paediatric medicine co-administration with vehicles, recommended in a commonly used paediatric and neonatal handbook, in addition to the information previously gathered from UK formularies. Multinomial logistic regression analysis was performed to further understand the biopharmaceutical basis of the choice of recommended vehicle for medicine co-administration.

Key findings: In this review, the recommended strategies for the co-administration of paediatric medicines with food and drinks were discussed and compared with relevant regulatory guidelines, according to globally used sources. Differences were identified in the type of vehicles globally recommended for medicine co-administration. Ultimately, a statistical model was developed which provided an understanding on which vehicle is recommended for use with drugs/formulations, with basis on their biopharmaceutical properties.

Conclusions: Overall, this review highlights the areas where further information is needed to support standardised procedures and guide the recommendation of age-appropriate and acceptable vehicles for use in the co-administration of paediatric medicines. Approaches such as the statistical model developed in this study could be used towards the creation of unified guidelines, where vehicle selection can be made based on biopharmaceutical characteristics. Ultimately, unified requirements are needed for harmonisation of this practice of co-administration with vehicles.

1. Introduction

A shift has been observed towards the development of user-friendly, preservative-free, taste-masked formulations (*e.g.* multiparticulate single-use solid dosage forms) for the paediatric population (1-4). However, the heterogeneity of the paediatric population hinders medicine development (2, 3). Consequently, lack of medicines designed and studied for use in paediatrics is still an issue, and in many therapeutic areas the need for authorised paediatric formulations remains (2). When age-appropriate licensed formulations are not available, there are several options for providing paediatric patients with suitable treatments. These include: (i.) seeking a licensed therapeutic alternative, (ii.) importing products authorised in other countries (which can be costly, time-consuming, and often subject to strict regulations), (iii.) compounding medicines within the pharmacy (*i.e.* preparing an unlicensed medicine to meet specific patient needs) or (iv.) manipulating licensed dosage forms (5-7).

Drug manipulation is a widely spread, common practice for drug administration and refers to handling of medicines to make them suitable for intended administration, for example when a specific dose not available is needed, to improve taste and/or patient acceptability and compliance (5). Examples of medicine manipulation include dividing/crushing a tablet, opening a capsule and emptying its contents, making serial dilutions, mixing syrup into a crushed tablet to prepare an extemporaneous preparation, and mixing a medicine with food or drinks (vehicles) to aid administration. Several risks have been associated with drug manipulation practices, including inconsistent results in terms of dose accuracy and possible effects on drug stability, solubility and bioavailability (7-10). Ultimately, these practices may lead to sub therapeutic or even toxic drug levels and/or increase the risk of side effects, which raises safety concerns (1, 7, 11, 12). Therefore, there is a need to evaluate the impact of drug manipulation practices and standardise recommendations and administration procedures to reduce the risks associated with medicine manipulation.

The most practiced manipulation technique to facilitate paediatric administration is to mix a dosage form with vehicles (12, 13). Small amounts of food or drinks can be used as vehicles for oral administration of medicines, provided they do not alter formulation performance, and are compatible and suitable for use in the targeted

patient age group (5, 14). Therefore, when this practice is intended, assessment of quality attributes of the mixture formulation-vehicle should be performed (*e.g.* potency assay, and *in vitro* dissolution/release studies) (5, 14).

Clear instructions on the optional use of vehicles to facilitate medicine administration, should be included in the labelling, summary of product characteristics (SmPC) and patient information leaflet (PIL) of the commercial formulation (5, 14). However, many factors such as seasonal, regional and climate conditions as well as age-related characteristics will influence vehicle composition or preference, respectively (7). For example, diet preferences will change depending on the age group (*e.g.* younger age groups have mostly a liquid diet and so mixing with a solid food would not be an option), country and physiologic characteristics (*e.g.* swallowability problems in very young ages) (6). Thus, the best candidates for use in practice are vehicles with relatively small fluctuations in their macronutrient composition and physicochemical characteristics, such as vehicle viscosity and pH, and binding/chelation characteristics. Moreover, vehicle candidates should be screened concerning their interaction with drug and formulation properties and their adequacy to the target age group (5, 14).

To standardise quality and availability of paediatric medicines, global initiatives have been undertaken. In the EU, the European Committee on Pharmaceuticals and Pharmaceutical Care (CD-P-PH) and the European Directorate for the Quality of Medicines & HealthCare (EDQM) have recently launched an initiative towards the compilation of a pan-European Paediatric Formulary, consisting of monographs for extemporaneous formulations, based on national or regional information (15, 16). This Formulary is intended to give indications on the preparation of extemporaneous formulations for paediatric medicines and harmonise medicine administration practices. It should be noted though that information regarding formulation co-administration with food and drinks is not included in the pilot monographs available (15, 17).

In practice, recent studies have shown that medicine co-administration with vehicles is often performed without following recommended procedures (7). Parents, carers and healthcare professionals often choose or let the child choose the food or drink used for medicine co-administration, without following the recommendations stated

on the PIL or SmPC of the medicine (7, 12, 13). The implications of the uninformed use of vehicles for medicine co-administration on drug safety and efficacy are often not taken into consideration.

Recommendations for mixing oral drugs with vehicles for paediatric administration, as described in national and hospital formularies from the UK, have been recently reviewed (7). Differences in the type of vehicles recommended and used in current practice were identified, and it was also revealed that vehicle recommendations are made on a case-by-case basis, without a clear scientific rational behind the choice of vehicle and/or depending on the patient and/or administration setting (*e.g.* hospital or home). The importance of considering the possible physicochemical or bioavailability changes that may occur from the co-administration of medicines with vehicles in the paediatric population were highlighted.

In this review, the vehicles currently recommended to be used for medicine co-administration to paediatric patients are discussed on a global perspective. Firstly, vehicle recommendations as reported in a paediatric handbook frequently used in clinical practice (in the US and other countries) were compared to previously gathered information from other formularies. Secondly, differences between recommendations were evaluated. Similarly to our previous review (7), the type of vehicles recommended to be mixed with medicines were correlated to the type of formulation and the BCS class of the drug, in order to reveal the biopharmaceutical aspects of the recommended administration strategies. Current administration practices were also compared with the relevant regulatory guidelines in order to assess possible differences and clinical consequences. Finally, a statistical model was developed in order to understand the choice of vehicle type recommended, based on the characteristics of the drug/formulation.

2. Methods

A focused search was performed on the vehicles that are globally used for mixing with dosage forms for paediatric administration. The Lexicomp Neonatal and Paediatric Dosage Handbook (18) (referred to as *Lexicomp Handbook* in this review) was identified as a source of information. In clinic, it is a valuable point-of-care

dosing resource, designed to support medical professionals managing paediatric and neonatal patients. For the purpose of this study, the drug monographs included in this handbook were screened, with emphasis on the 'mode of administration' section. Drugs were included in the review if co-administration dosage forms with food, drinks or meals were suggested. Drugs for which recommendations were to take the formulations 'with or without food/meals' or 'without regards to food/meals' were also included. Because this review focuses on a specific type of medicine manipulation (*i.e.* mixing the drug with vehicles), drugs for which only manipulation techniques were referred and/or drugs for which only water was included as an administration vehicle were not included. The information gathered from this new source was combined with information previously gathered, for a global evaluation of practices and vehicle recommendations (7, 19, 20).

Multinomial logistic regression analysis was performed to further understand the biopharmaceutical basis of the choice of recommended vehicle for medicine co-administration, using XLSTAT® software (an Add-In for Excel, Microsoft®). This statistical method is used to understand the effect of a series of variables on an unordered qualitative response variable (a variable which can take at least two values) (21). The statistical analysis was performed to predict the effect of drug and formulation characteristics (namely, drug logP, drug aqueous solubility, drug Biopharmaceutical Classification System [BCS] class and formulation type) on the choice of vehicle type (response variable; drinks or soft foods) recommended to be mixed with paediatric medicines. The explanatory variables used were: high/low drug solubility (presented as *HighSol* and *LowSol*, respectively), formulation type (*Solid/Liquid*), and drug logP (presented as *Hydrophilic* for logP < 3 and *Lipophilic* if logP > 3). The statistical analysis was described by an equation, which was built relatively to the response variable chosen as reference category (in this case, drinks as the vehicle type recommended for drug administration). The obtained equation was a model of the probability associated to the type of recommended vehicle being 'drinks', depending on the values of the explanatory variables (21). If the estimated probability of the event occurring is greater than or equal to 0.5 (better than even chance), the event is classified as occurring. If the probability is less than 0.5, the event is classified as not occurring (in this case, the vehicle type recommended is not drinks, but soft foods). To build and validate the analysis, a total of 430 drug-

formulation-vehicle combinations were considered; these were divided into two groups: 300 combinations were used for the construction of the model, and 130 for the validation of the model.

3. Results

3.1 Mixing medicines with food and drinks in the context of their physicochemical properties

The Lexicomp Handbook lists recommendations for the administration of paediatric medicines, providing information on which food or drinks to use for medicine co-administration, when applicable (18). Appendix I lists the 407 drugs (out of 1054) included in this handbook that are recommended to be mixed with food and drinks prior to oral administration, in addition to the recommended vehicles for administration. The BCS class of the drug, aqueous drug solubility and drug ionisation characteristics were added to the information collected from the Lexicomp Handbook. Eight formulation types were identified: *tablets, capsules, ampoules, granules*, *powder*, *solutions*, *syrup* and *suspensions*. The type of vehicles recommended were categorized into *Soft foods* (*e.g.* yoghurt, applesauce, fruit puree), *Drinks* (*e.g.* milk, juices, formula) and *Others* (*e.g.* meals, food, suspending agents/syrups). Recommendations for administration with water were only noted when it was an alternative to other drinks. Specific recommendations included in the drug monographs were noted, such as unsuitable vehicles, further examples of suitable vehicles for mixing, and/or the acceptable amount of vehicle to administer. Drugs for which simple manipulation techniques were given without specific suggestions for mixing with vehicles (*e.g.* tablets 'may be crushed or dissolved') were not included. Drugs for which recommendations were to take the formulations 'with or without food/meals' or 'without regards to food/meals' were included; for simplification, these recommendations will be denoted as 'with or without food' in this review. It is worth noting that improving palatability/taste was indicated in 2 cases, lopinavir/ritonavir tablets and ritonavir liquid, as a reason for co-administration with a vehicle. However, this information was not revealed for the remainder of the drugs. Similarly, decreasing gastrointestinal (GI) distress was

indicated in 23 % (94/407) of the cases as a reason for medicine co-administration with food/drinks.

The drugs previous previously collected from other sources (19, 20) were added to the database for further analysis, in order to obtain a global understanding of the vehicle recommendations. The database used for analysis encompassed 428 drugs, of which 77 % (331/428) were included only in the Lexicomp Handbook, 5 % (21/428) only in the UK formularies and 18 % (76/428) in sources from both settings, although sometimes with different recommendations.

The BCS is a regulatory framework for oral drug products for adults, which categorises drugs based on their solubility and permeability (22). 61 % of the 428 drugs gathered were classified into one of the four BCS classes, based on information (published studies or predictive values) regarding the solubility and permeability of the drugs (Figure 2.1). It was shown that most drugs suggested to be co-administered with food and drinks were drugs with high permeability (19.6 % and 20.1 % belong to BCS class I and II, respectively), whereas only 14.5 % of the drugs belonged to BCS class III and 6.8 % to BCS class IV. It should be noted that unclassified drugs (in terms of BCS class) were not considered for further analysis.

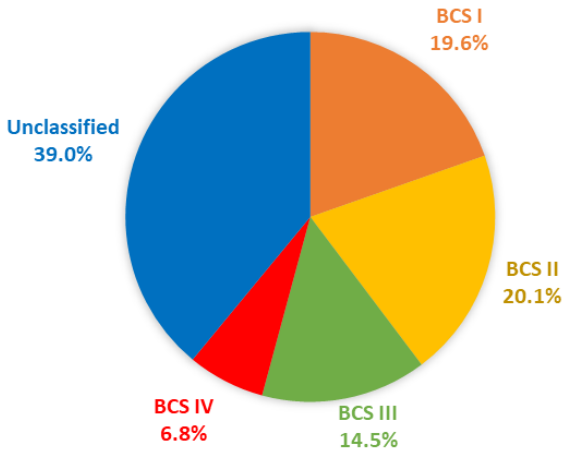


Figure 2.1. BCS classification of the drugs recommended to be mixed with food and drinks

Mixing a paediatric medicine with food and drinks has been shown to affect its biopharmaceutical characteristics (7). To further investigate this, analyses were carried out to reveal potential correlations between the BCS class of the drugs, the

type of formulation administered, and the type of vehicles recommended for mixing with the drug.

3.1.1 BCS class of the drug *vs* formulation type

The relationship between drug BCS class and the type of formulation co-administered with food or drinks is shown in Figure 2.2. Tablets and capsules were shown to be the predominant dosage forms mixed with foods or drinks, for drugs of the four BCS classes. BCS class I products formulated as solutions and BCS class IV products formulated as suspensions are also commonly recommended to be mixed with foods or drinks.

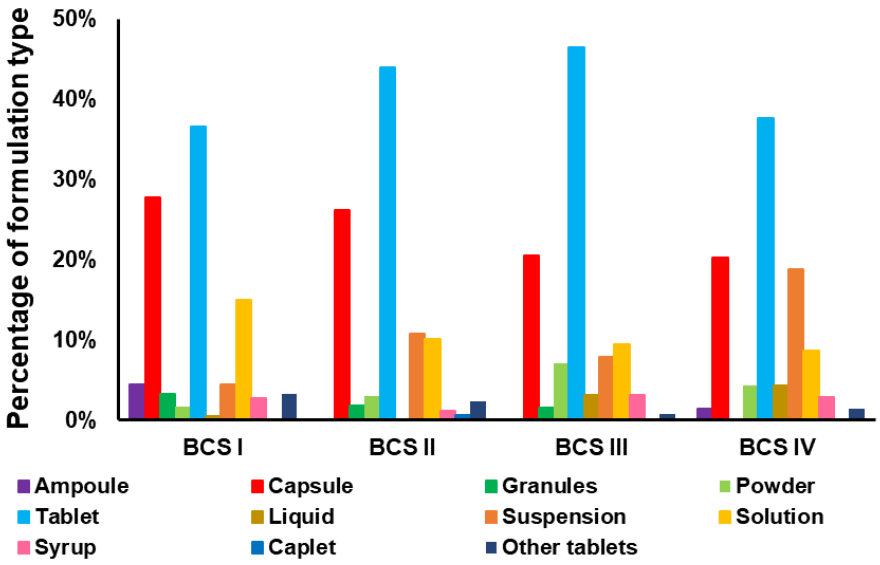


Figure 2.2. Percentage of type of formulation in relation to the BCS class of the drug recommended to be mixed with food and drinks

3.1.2 BCS class of the drug *vs* type of vehicle

Figure 2.3 shows the prevalence of the type of vehicle used for drugs belonging to each BCS class. Vehicles of all types are recommended for mixing with all BCS classes. Soft foods are the least commonly suggested to be mixed with paediatric medicines, particularly with BCS class III and IV drugs. Meals/foods and syrups (classified as *others*) are the most commonly recommended vehicles for co-

administration with drugs belonging to BCS class I, II and IV. Despite this, recommendations are often not clear on the mixing process, the type and the amount of food/meal to use. For BCS class III drugs, the most commonly suggested recommendation is to mix 'with or without foods/meals', which is a dubious recommendation regarding whether it is possible to mix the drug with vehicles. Drinks are commonly suggested to be mixed with paediatric medicines for drugs of all BCS classes.

Recent studies have assessed the physicochemical properties of vehicles commonly reported to be mixed with paediatric medicines for co-administration (23, 24). Distinguished differences between the physicochemical properties (*e.g.* pH, surface tension, osmolality, viscosity, buffer capacity) and macronutrient composition of different food and drinks were observed, both among vehicles of different types (drinks *vs* soft foods) and within vehicles of the same subtype (*e.g.* different formulas). These differences between vehicle properties affect drug solubility and dissolution properties, particularly of poorly soluble drugs (25-27). For example, solubility studies of mesalazine and montelukast, performed in drinks and soft foods, resulted in considerably different drug solubility values in each vehicle, being significantly affected by the physicochemical properties and macronutrient composition of the vehicles (25-27). This vehicle-dependent impact on drug properties could compromise drug bioavailability and should be taken into consideration during paediatric product development.

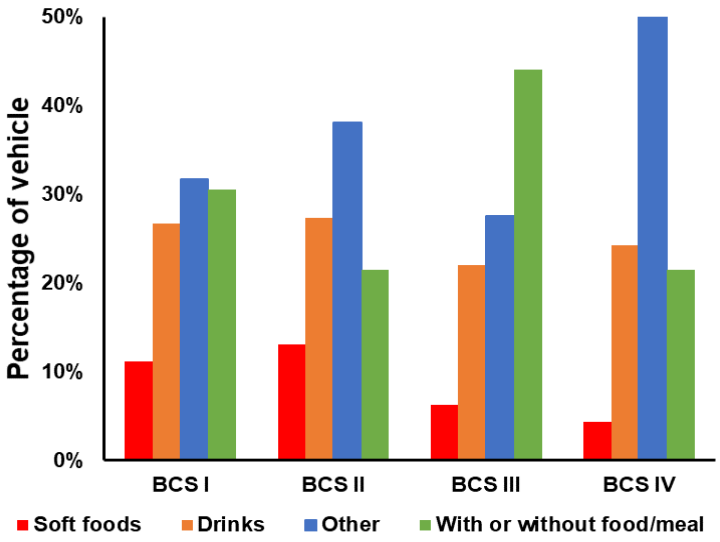


Figure 2.3. Percentage of the type of vehicle in relation to the BCS class of the drug recommended to be mixed with food and drinks

3.1.3 Type of vehicle recommended *vs* type of formulation

The relationship between the type of vehicle recommended for medicine co-administration and the type of formulation is presented in Figure 2.4. Ampoules for IV administration are mainly recommended to be mixed/diluted with drinks and administered orally. In some cases, such as for topotecan ampoules, the recommendation is to mix with acidic drinks (*e.g.* apple juice); however, this type of recommendation should not be generalised since depending on the drug this practice might affect drug stability. Soft foods are mainly suggested for mixing with capsule formulations. All vehicle types are reported for mixing with liquids, solutions and suspensions. Apart from soft foods, all vehicle types are recommended to be mixed with syrups. Tablets are recommended to be mixed with all vehicle types, with a high prevalence of mixing with meals/food and with suspending agents/syrups for extemporaneous preparations. Mixing 'with or without foods/meals' is reported for all formulation types, except granules and caplets. It should be noted that for several cases, recommendations were made to mix the suggested vehicles with oral dosage forms, and so all the oral drug formulations listed in the Lexicomp Handbook as available were considered. This suggests that recommendations were possibly made based on physicochemical properties and characteristics of the drug, and not formulation.

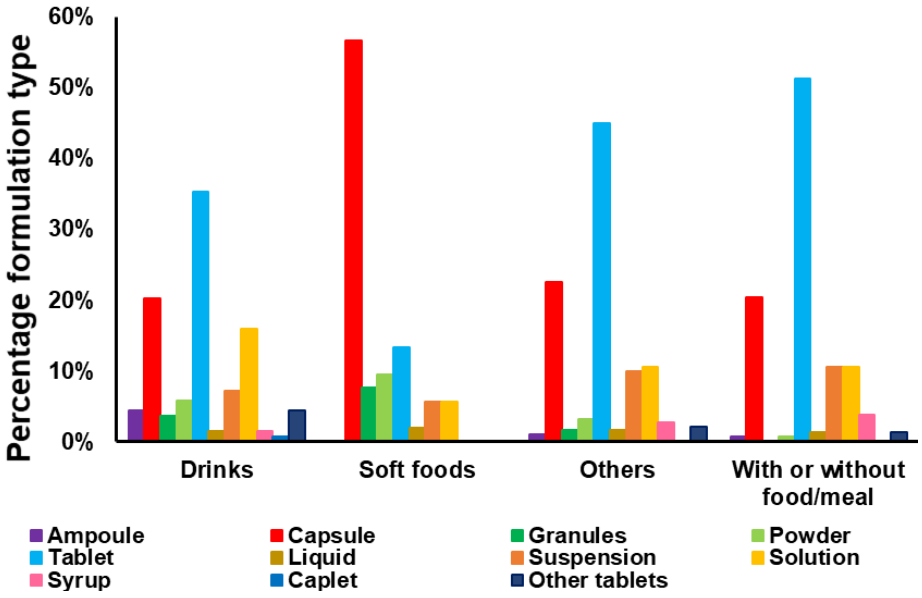


Figure 2.4. Percentage of the type of vehicle recommended in relation to the type of formulation.

3.2 Effect of drug/formulation properties on the choice of the recommended vehicle

Although there have been many reports on the use of food and drink vehicles to facilitate administration of paediatric medicines, there are still major gaps in the knowledge of the scientific rationale for choosing which vehicle is appropriate (7, 14).

Multinomial logistic regression analysis was performed to investigate the relationship between drug/formulation variables and the type of vehicle recommended (drinks, soft foods). The statistical model is described by the following equation (Eq. 2.1):

$$Pr_{(drinks)} = 1/\left[1 + e^{-(811.400+0.113*LowSol+0.460*Solid-\ 0.143*Lipophilic)}\right] \quad \text{(Eq. 2.1)}$$

where, $Pr_{(drinks)}$ is the probability of the vehicle type recommended to be drinks, and LowSol, Solid and Lipophilic can take the values of 1 or 0 depending on whether the drug/formulation has those characteristics or not, respectively.

For example, for a lipophilic drug (Lipophilic = 1), with high solubility (LowSol = 0) and formulated as a tablet (Solid = 1), the probability of the vehicle type recommended to be drinks is 0.59.

Model validation was performed by comparing the type of vehicle recommended in the formularies and the vehicle type predicted by the model equation, using 130 drug-formulation-vehicle combinations as validation sample. In 60 % of the cases, the multinomial logistic regression model could predict correctly the vehicle type recommended, according to drug and formulation characteristics.

The standardised coefficients of each studied variable are presented in Figure 2.5 and reveal that formulation type is the variable with most impact on the choice of vehicle type recommended ($p < 0.05$).

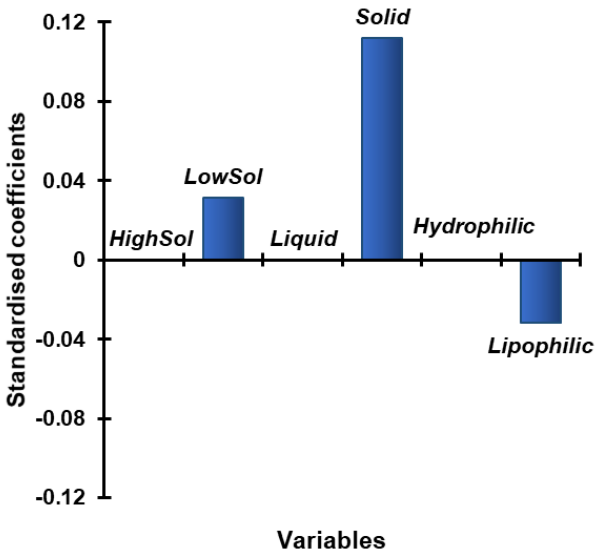


Figure 2.5. Standardised coefficients corresponding to the variables studied for the multinomial logistic regression model constructed.

Overall, this analysis was a first approach towards defining a correlation/rational between the type of vehicle suggested for mixing and the drug and formulation properties. The developed model provides an insight on which vehicle type is recommended for use with basis on the biopharmaceutical properties of the drugs/formulations. It has a reasonably good predictive ability, with predicted and calculated vehicle recommendation in the test set showing good agreement. Nevertheless, given that the model is currently based on a dataset comprising a limited number of sources, further work is required to verify and extend the approach. Despite its limitations, the analysis described provides information to generate awareness and discussion towards co-administration practices of paediatric

medicines, within the clinical and scientific communities. In the future, it would be useful to include information from other formularies not identified in this review to further refine and validate the model constructed.

4. Discussion

4.1 Discrepancies in recommendations reported − a global perspective

In this review, the availability of drug products recommended to be mixed with food and drinks was assessed using two datasets: (i.) the list of drugs gathered after consulting the Neonatal and Pediatric Dosage Handbook (18), and (ii.) the database previously collected in Chapter 1 from two sources (British National Formulary for Children (19) and a Hospital Formulary (20)). Over half of the drugs for which mixing with a vehicle was suggested in the Lexicomp Handbook were not included in the UK formularies. Although it is not completely clear how the recommendations were established, a possible explanation for this is the discrepancy observed in the number of drugs included in the sources (*e.g.* the Lexicomp Handbook included 1054 drug monographs whereas the UK formularies included less than half that number). In addition, 47 % of the drugs were included in both datasets, but with no vehicle suggestions for medicine co-administration in the UK. For example, terbinafine is recommended to be mixed with non-acidic foods in the Lexicomp Handbook, but not in the UK formularies even though it was included in the formularies consulted. A more concerning issue arises in the cases of tenofovir disoproxil fumarate, sodium phenylbutyrate and risperidone (Table 2.1). In the first case, the BNF-C and Lexicomp Handbook warn against mixing with liquids, whereas mixing of the granules with orange juice or water is advised in the Hospital Formulary. In the case of sodium phenylbutyrate, the Lexicomp Handbook advises against mixing with acidic drinks whereas fruit juices are recommended in the UK formularies. Similarly, risperidone formulations are suggested to be mixed with coffee in the formularies, whereas this drink is advised against mixing with the drug in the Lexicomp Handbook.

Table 2.1. Differences in recommendations between the different sources consulted

Drug	Sources	
	Lexicomp Handbook (18)	**BNF-C (19) and Hospital Formulary (20)**
Risperidone	Mix with water, orange juice, or low-fat milk **Do not** mix with coffee or tea	Mix with milk, juice, **coffee, tea,** fruit juice, orange juice (20); **Mix with non-alcoholic drinks except tea** (19)
Sodium phenylbutyrate	**Avoid mixing with acidic beverages** *e.g.* most fruit juices or colas, food, meal or feeding	**Mix with fruit juice** (19), meals, milk (20)
Tenofovir disoproxil fumarate	**Do not mix with liquids** Mix with 2-4 ounces of applesauce, baby food, yoghurt	Mix with soft foods *e.g.* yoghurt, applesauce (19); **Mix with orange juice** (20)

4.2 Medicine co-administration with food and drinks – from regulatory guidance to reported recommendations and practices

The widespread use of *off-label* and unlicensed medicines for the paediatric population confirms that the currently available commercial products do not meet the needs of this population. Medicines are often manipulated prior to administration due to unacceptability of the dosage form to the patient or unavailability of the needed dose. Medicine co-administration with vehicles is the most practiced manipulation strategy in paediatrics; however, no recommended testing methodology or uniform criteria to define what is classed as globally acceptable vehicle for the different paediatric age groups (*e.g.* in terms of flavour, texture and composition) have been set to predict the possible impact of medicine co-administration with vehicles on drug product performance (6, 10, 28).

Current guidance has begun addressing the recommended strategies for paediatric medicine development, acceptability and administration, with special emphasis on co-administration of medicines with food and drinks (5, 14, 29). The most recent example is the Food and Drug Administration (FDA) draft guidance released in 2018, which recommends vehicle selection approaches and *in vitro* testing for co-administration of paediatric medicines (14). The three main purposes of this draft guidance are: (i.) to give recommendations on vehicle selection, (ii.) to describe standardised *in vitro* methods for evaluating vehicle compatibility, and (iii.) to provide suggestions on product labelling for communication of acceptability (or unacceptability) of vehicles intended for mixing with the medicine.

In the following subsections, the considerations provided in current regulatory guidance, regarding vehicle selection and testing, will be discussed and compared to reported recommendations gathered from the sources consulted and reported healthcare practices (5, 14, 29).

4.2.1 Vehicle selection: *in vitro* assessment of drug product-vehicle compatibility and use in practice

Regulatory guidance states that *in vitro* compatibility studies should be performed when co-administration of medicines with food or drinks is intended. It is recommended that comprehensive suitability determinations are conducted to evaluate the potential impact of the proposed vehicle on drug behaviour and provide guidance on the appropriate vehicle to use in the target age group. These assessments include: (i.) potency assays, to quantify the amount of drug in the drug product-vehicle mixture, evaluate drug product performance and support the recommended use time of the mixture after preparation; (ii.) integrity testing, to verify if the drug substance quality attributes are maintained after mixing with a vehicle; (iii.) stability assessments, to support instructions for the mixture preparation and labelled use time of the mixture; (iv.) dose uniformity/homogeneity testing; and (v.) drug release/dissolution testing, to determine possible changes in drug behaviour (*i.e.* release/delivery from the drug product and drug dissolution).

Ideally, food and drinks which have been proven to cause no appreciable effect on medicine performance should be proposed as vehicles. It is advised that drug product information (product labelling, SmPC, PIL) should also include instructions on vehicles found unacceptable, including the rationale for avoiding their use as vehicles for medicine co-administration (14). For example, a soft food like applesauce should be deemed inappropriate if the targeted patient population are infants still consuming a liquid diet, even if the mixture vehicle-drug product is physicochemically stable (14).

In practice, according to the administration techniques reported by healthcare professionals, carers and parents, it is common to mix formulations with foods and drinks that have not been evaluated (*i.e.* not mentioned in the SmPC, PIL or product labelling) (12, 13, 30). Consequently, an unsuitable vehicle might be used, which

may lead to possible changes in drug performance *in vivo*. This might be critical since different food and drinks can have dissimilar effects on a paediatric medicine due to their physicochemical properties and might significantly impact drug bioavailability and, consequently, therapeutic efficacy (8, 31). For example, crushing of gastro resistant dosage forms, such as NSAID drugs, to mix with a vehicle can alter drug absorption and efficacy and/or cause irritation of the gastrointestinal mucosa and, ultimately, may increase the risk of side effects, such as formation of gastrointestinal ulcers. Stability and compatibility studies of tegaserod from crushed tablets in soft food and drinks (water, apple juice, orange juice, and applesauce) revealed that while the drug was stable in and compatible with these vehicles, the dissolution profiles of the crushed tablets in orange juice and applesauce were not comparable with those of intact tablets (32).

The FDA draft guidance provides a list of 27 vehicles commonly used for medicine co-administration (reproduced in Table 2.2), which includes the most predominant vehicles used in both inpatient and outpatient settings, such as drinks (*e.g.* fruit juices), yoghurts and banana purée (13, 30). In the formularies consulted (18-20), a predominant vehicle type is not recommended, probably due to the lack of rational behind vehicle selection. When comparing the information gathered from the consulted formularies/handbooks with reports from healthcare professionals and the FDA draft guidance, several discrepancies were found in recommendations (7, 14, 18). For example, only 44 % (12/27) of the vehicles listed in the FDA draft guidance were referenced more than 5 times in the sources consulted, 15 % (4/27) of vehicles are referenced between 1 and 3 times in the sources consulted, and 41 % (11/27) are not specifically mentioned as recommendation vehicles. Banana purée is one of the vehicles included as being frequently used in practice (both according to reports from healthcare professionals and the FDA guidance) but is not clearly stated as an example in any of the sources consulted (13, 18-20). Concerning issues may arise from these differences; for instance, juices are frequently used vehicles in practice but, in the formularies consulted, using fruit juices for medicine co-administration is advised against in the cases of several drugs (*e.g.* bosentan tablets, ethambutol tablets and etravirine tablets) (Appendix I). Moreover, although vehicles with higher viscosity are frequently used (*e.g.* banana puree, yoghurt), vehicle

viscosity has been shown to negatively affect the dissolution of different drugs (26, 27, 33).

Table 2.2. Commonly used soft foods and drinks (reproduced from (14))

Soft foods	Drinks
Apples (puree)	Apple juice
Applesauce	Buttermilk
Baby food (unstrained)	Coconut milk
Bananas (puree)	Cranberry juice
Carrots (puree)	Water
Chocolate pudding	Grapefruit juice
Fruit jellies	Infant formula
Fruit jam	Milk
Honey	Orange juice
Maple syrup	Pineapple juice
Orange marmalade	Soybean milk
Peanut butter	
Rice pudding	
Strawberries (puree)	
Strawberry jam	
Yoghurt	

Overall, in practice there seems to be no clear rational behind vehicle selection for use in medicine co-administration. For most drugs, information of possible co-administration with vehicles is not included in the product information (labelling, SmPC nor PIL); therefore, the possible impact of this practice on drug performance is often unaddressed (6, 7, 10, 34). Recognising this, the FDA draft guidance establish a clear rationale on the most correct approach for vehicle selection and standardised age-appropriate testing methodologies. Vehicle selection and age-appropriate compatibility methodologies of drug-formulation-vehicle should be addressed during paediatric product development, to understand the vehicle impact on the drug product and the implications of medicine co-administration on drug clinical outcomes. In this context, a decision tree for vehicle selection is available on the FDA draft guidance, presented as a recommendation and not a mandatory requirement during paediatric drug development (14). A complicating factor for the establishment of uniform practices are the absence of a correct assessment of the acceptability of the product-vehicle mixture, in terms of flavour, texture, mouthfeel, and age-related responses to physical characteristics of the mixture (34). For example, pharmacokinetic studies have been performed with applesauce, which is

not always well accepted among the paediatric population (*e.g.* in younger age groups whose diet consists mostly of liquids) (23). Therefore, the potential acceptance of the paediatric population and vehicle uniform composition in different countries should be a focus point in the recommendations. Ultimately, it is necessary to fully establish and regulate assessment criteria and perform appropriate studies to provide better guidance for healthcare practitioners, patients and carers regarding medicine co-administration with vehicles in the paediatric population.

4.2.2 Volume of vehicle

The suggested volume of vehicle to use for mixing with solid oral dosage forms should take into consideration the age, size, and average consumption of the vehicle by the targeted patient population. For example, children younger than two years old may not be able or willing to ingest large volumes of drinks or soft foods at one time. Regulatory guidance from both the FDA and the European Medicines Agency (EMA) states that the typical volume of vehicle administered to a paediatric patient should be 'swallowable in one unit' to ensure administration of the complete drug dose, whilst facilitating swallowing and providing acceptable taste-masking (14, 29). Volumes between 5 and 15 mL have been proposed as acceptable and are normally preferable, which means that exploring alternate vehicles should be considered if a large volume is required (34). However, in adult studies recently conducted to investigate the administration of paediatric formulations mixed with vehicles, the volume of vehicles used varied between one tablespoon and 120 mL (6). Moreover, when looking at the recommendations gathered (Appendix I), it is observed that very different volumes of vehicles (ranging from 5 mL to 200 mL) are suggested to be mixed with the different drugs, although no justification is provided for the suggestions. For example, imatinib tablets 100 and 400 mg can be mixed with 50 and 200 mL of water or apple juice, respectively; lansoprazole capsules can be opened and mixed with 60 mL of juice or 1 tablespoon of soft foods; topotecan capsules can be opened and mixed with 30 mL of juice; and pantoprazole suspension can be mixed with 5 mL of juice.

The use of different volumes of vehicles can be prejudicial for the clinical outcome. For example, using a large amount of vehicle (*e.g.* one pot of yoghurt) might lead to

decreased accuracy in dose delivery, especially if the whole product is not consumed; conversely, use of a very small volume of vehicle (*e.g.* less than 5 mL) might not properly improve the palatability of the medicine and result in the patient refusal to consume it. Thus, further studies should be conducted towards defining age-appropriate volumes to consume, and a mandatory regulatory statement concerning the appropriate volumes for product testing should be provided to ensure a more unified approach.

4.2.3 Mixture preparation and handling

Standardisation of the preparation and use instructions for the drug product-vehicle mixture is important, as ambiguity in instructions or incomplete information can lead to unintended outcomes, including decreased accuracy in dose delivery and/or misuse of the drug product. Therefore, the FDA draft guidance states that the complexity of the preparation, homogeneity of the mixture, and handling procedures should be considered by the manufacturer (14). One idea that has been proposed to facilitate administration, whilst ensuring dosing accuracy, is to include an oral syringe or measuring spoon with the drug product along with clear use instructions to avoid administration errors (14).

In practice, no standardised rational seems to be used for administration practices of medicines to paediatrics. Drug manipulation practices as reported by parents, carers and healthcare professionals in inpatient and outpatient settings have been recently evaluated (12, 30, 35). For example, in a study recently conducted in the Netherlands, it was revealed that only 55 % of medicines were manipulated according to the instructions or recommendations of the SmPC or PIL (30). The main reasons for drug manipulation were found to be dose adjustment, taste improvement or feeding tube administration, with 52.3 % of the nurses interviewed admitting to having deviated from hospital protocols for manipulation (30). Similarly, manipulation of oral dosage forms has been shown to be common practice among parents, carers and healthcare professionals in other paediatric hospitals of different countries (*e.g.* UK, Australia) (12, 13, 35).

In general, the predominant reasons for manipulation have been shown to differ between the inpatient and outpatient settings. Manipulation by parents and carers is

usually performed for taste and dose adjustment, whilst healthcare professionals most often use manipulation for administration through a feeding tube, or for dose reduction (30, 36, 37). This difference probably results from: (i.) the more extensive formularies of inpatient pharmacies, which allow a more precise dosing with compounded dosage forms of different strengths, clinically supported by vehicle recommendations and (ii.) the higher prevalence of feeding tubes in the inpatient setting (30, 36). Regardless of the setting, the method used for mixture preparation and handling can differ depending on the person performing it, which can lead to dose accuracy inconsistencies (7). The risk of errors related to the drug manipulation will also increase if incorrect information is transferred from the healthcare professional to the parent and carer.

Overall, differences are still observed between current guidance recommendations and reported administration practices. This highlights the need for additional in-service training of the healthcare professionals, and consequently of parents and carers, regarding drug manipulation in order to fully harmonise medicine co-administration practices and avoid potential issues in drug product performance.

4.2.4 Time between preparation and administration of the mixture

The FDA draft guidance states that the drug product-vehicle mixture should exhibit no change in potency (as determined by a validated assay) nor in drug release characteristics over the time period proposed in the product information (14). It is generally recommended that prepared drug product-vehicle mixtures should be administered immediately or as directed in the product information, in order to avoid potential dosing errors and/or microbiological contamination of the mixture (14). The proposed time frame for administration of the mixture should be supported by product quality assessments in which the physicochemical stability of the mixture is ensured. If the mixture is intended to be used more than 2 h after preparation, microbiological testing should be also carried out (14).

In practice, information regarding the time frame for use of the mixture is often not indicated. Analysis of the recommendations gathered in the sources consulted, as well as recent reports on common practices in healthcare settings, revealed that information regarding the importance of immediate preparation is not provided for

most of the drugs suggested to be mixed with vehicles (7, 18). For example, this information was only available for 2 of the 408 drugs collected from the Lexicomp Handbook (Appendix I) (7, 18). These were: amoxicillin tablets (mixture should be administered 'immediately'), and ivacaftor granules (mixture should be consumed 'within 1 h').

The time between the preparation and administration of the mixture may influence drug stability, solubility and dissolution and, subsequently, its oral absorption. In recent studies, we have assessed the effect of delaying the testing of drug product-vehicle mixtures (by 4 h after their preparation) on the stability and dissolution of two poorly soluble compounds (mesalazine and montelukast) and their formulations (26, 27, 38). It was revealed that drug loss could occur to a small extent (< 15 %) in a time dependent manner and, consequently, concluded that administration of the mixtures should ideally be performed immediately after preparation, or at least within 4 h of preparation. An immediate administration of the mixtures would not only avoid potential drug/formulation stability issues and increased risk of drug precipitation, but also prevent other vehicle-effects on drug dissolution (*e.g.* increased solubilisation and wetting of the formulation). Other potential consequences are the increase of risk of adverse side effects, depending on the pharmacological category of the drug (33, 39).

Overall, when mixing with a vehicle is intended, information on the time for administration of the mixture should be provided to ensure proper administration of the manipulated dosage form, while guaranteeing drug safety and efficacy. The establishment of unified, global practices would be helpful in avoiding possible, significant clinical outcomes.

4.2.5 Information required for clinical practices of co-administration with food and drinks

PILs should provide enough information to ensure that the healthcare provider, patient, parent or carer have the essential knowledge required for appropriate use of the recommended vehicles. In regulatory guidance, a list of recommended information to include in the product information is given, and includes: (i.) recommended vehicle type, (ii.) detailed information on the vehicle to use, including

volume and temperature, (iii.) recommended critical manipulations (*e.g.* opening a capsule and emptying its contents or crushing a tablet), (iv.) information on vehicle compatibility and mixture administration (including a succinct summary of compatibility/suitability data), and (v.) a rationale for avoiding certain vehicles (5, 14, 29).

In reality, this information is scarce for most drugs, hindering the informed administration of acceptable vehicle-medicine mixtures to paediatric patients (7, 30, 34). In addition, even when food-drug interactions are known to the healthcare professional, it is not always possible to administer the drug with acceptable vehicles due to limitations on which vehicles can be used for administration through enteral feedings (36, 40).

4.2.6 Clinical evaluation of medicine co-administration practices

Although regulatory bodies acknowledge the importance of conducting paediatric studies and their benefit for the patients, these are not considered necessary (4). In the EU, an optional *in vivo* study to evaluate this practice is suggested in the EMA guideline on pharmaceutical development of paediatric medicines (29). This can be a separate bioequivalence study in adults or, alternatively, paediatric clinical trials can be conducted with the vehicle of choice. Extrapolation of food-effects observed in adults into paediatric subpopulations is an unexplored and complex area due to physiological and anatomical differences between the two populations. This may result in different food effects in the paediatric population compared to adults (41, 42). Paediatric clinical trials conducted for vehicle assessment are limited; for example, suitability tests were performed on the co-administration of montelukast paediatric formulations with formula and applesauce (6). Paediatric clinical studies are generally conducted to investigate PK do not always reflect paediatric administration practices and, consequently, the clinical impact of the administration of paediatric medicines with food and drinks is often not evaluated (43).

In the USA, the practice of mixing medicines with foods is described in the FDA guidance on Food-Effect Bioavailability and Fed Bioequivalence Studies; studies in healthy adult volunteers are usually requested and accepted and, additionally, *in vitro* and *in silico* tests can be accepted as supportive evidence (10, 43, 44). In this

context, a recent study described how *in vivo*, *in vitro* and *in silico* investigations were adjusted to existing knowledge available for two model drugs (one poorly and one highly soluble) (10). Drug stability when mixed with different vehicles was confirmed and suitable vehicles for co-administration were selected, following a combination of *in vitro* dissolution and drug solubility studies and *in silico* modelling (10).

Overall, investigation of vehicle suitability as part of paediatric clinical trials would provide the highest reliability in terms of product safety and efficacy. However, introduction of additional drug administration conditions and patient recruitment difficulties might further complicate the design, execution, interpretation of results, and, ultimately, the outcome of clinical studies. The use of *in vitro* and/or *in silico* age-appropriate predictive tools to aid understanding of formulation performance in paediatrics would be beneficial to understand the impact of medicine co-administration with vehicle, and age-related factors on drug behaviour. Furthermore, these tools could be used to predict *in vivo* clinical outcomes. Ultimately, the development and establishment of *in vitro* and/or *in silico* testing during paediatric drug development could help reduce the number of *in vivo* studies required for paediatric formulation development, and tackle ethical issues related to clinical research in the paediatric population (2).

5. Conclusions

In view of the prevalence of the practice of medicine co-administration with food and drinks in paediatrics, efforts should be made to reconcile the information available and provide clear, easily accessible information on vehicle suitability. However, information on the appropriate vehicle to use is still not available for many medicines, and no clear rational seems to guide vehicle recommendations. Published sources reporting this practice show a lack of standardisation in terms of vehicle recommendations, criteria defining vehicle acceptability, administration practices, and evaluation assessments. Moreover, the absence of mandatory status leads to differences between practice and recommendations, further hindering the establishment of uniform, acceptable administration techniques.

In this study, with the information gathered from available paediatric formularies, a statistical model was developed. This model provides an understanding on which vehicle type is recommended for use in medicine co-administration practices, based on the physicochemical and biopharmaceutical properties of the drug/formulation. The developed model has a reasonably good predictive ability, with predicted and calculated vehicle recommendations in a test set showing a good agreement. However, as the model is currently based on a dataset comprising a limited number of sources, further work is required to verify and extend this approach. This could serve as a starting point towards the development of unified guidelines, where selection of a vehicle can be made based on drug/formulation characteristics.

Overall, it is recognised that healthcare professionals would benefit from obtaining complete training on this practice in order to be informed on possible clinical outcomes and correctly train parents and carers. A consensus agreement between academia, the pharmaceutical industry and regulators would be welcomed to harmonise and standardise the methodology for vehicle compatibility assessments, and provide uniform and established, scientifically-based guidance.

Supplementary material

- *Appendix I*

References

1. Strickley RG, Iwata Q, Wu S, Dahl TC. Pediatric drugs - a review of commercially available oral formulations. J Pharm Sci. 2008;97(5):1731-74.

2. Ernest TB, Elder DP, Martini LG, Roberts M, Ford JL. Developing paediatric medicines: identifying the needs and recognizing the challenges. J Pharm Pharmacol. 2007;59(8):1043-55.

3. Ivanovska V, Rademaker CM, van Dijk L, Mantel-Teeuwisse AK. Pediatric drug formulations: a review of challenges and progress. Pediatrics. 2014;134(2):361-72.

4. Turner MA, Catapano M, Hirschfeld S, Giaquinto C. Paediatric drug development: the impact of evolving regulations. Adv drug deliv rev. 2014;73:2-13.

5. World Health Organization. Development of paediatric medicines: points to consider in pharmaceutical development (Working document QAS/08.257/Rev.3). 2011. http://www.who.int/medicines/areas/quality_safety/quality_assurance/Rev3-PaediatricMedicinesDevelopment_QAS08-257Rev3_17082011.pdf . Accessed 21 January 2016.

6. Guimarães M, Statelova M, Holm R, Reppas C, Symilllides M, Vertzoni M, et al. Biopharmaceutical considerations in paediatrics with a view to the evaluation of orally administered drug products–a PEARRL review. J Pharm Pharmacol. 2019;71(4):603-42.

7. Martir J, Flanagan T, Mann J, Fotaki N. Recommended strategies for the oral administration of paediatric medicines with food and drinks in the context of their biopharmaceutical properties: a review. J Pharm Pharmacol. 2017;69(4):384-97.

8. Chun AH, Erdman K, Zhang Y, Achari R, Cavanaugh JH. Effect on bioavailability of admixing the contents of lansoprazole capsules with selected soft foods. Clin Ther. 2000;22(2):231-6.

9. Belard S, Isaacs W, Black F, Bateman L, Madolo L, Munro J, et al. Treatment of childhood tuberculosis: caregivers' practices and perceptions in Cape Town, South Africa. Paediatrics and international child health. 2015;35(1):24-8.

10. Batchelor H, Kaukonen AM, Klein S, Davit B, Ju R, Ternik R, et al. Food effects in paediatric medicines development for products co-administered with food. Int J Pharm. 2018;536(2):530-5.

11. Richey RH, Shah UU, Peak M, Craig JV, Ford JL, Barker CE, et al. Manipulation of drugs to achieve the required dose is intrinsic to paediatric practice but is not supported by guidelines or evidence. BMC Pediatr. 2013;13(1):81.

12. Venables R, Stirling H, Batchelor H, Marriott J. Problems with oral formulations prescribed to children: a focus group study of healthcare professionals. Int J Clin Pharm. 2015;37(6):1057-67.

13. Akram G, Mullen AB. Paediatric nurses' knowledge and practice of mixing medication into foodstuff. Int J Pharm Pract. 2012;20(3):191-8.

14. Food and Drug Administration. Center for Drug Evaluation and Research, Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments - Draft Guidance for Industry. 2018. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM614401.pdf. Accessed 6 October 2018.

15. European Directorate for the quality of medicines and healthcare. A European Formulary for paediatric medicines - Rules and Criteria approved. 2016. https://www.edqm.eu/sites/default/files/press_release_european_paediatric_formulary_january_2016.pdf. Accessed 26 January 2016.

16. Leutner D. A pan-European paediatric formulary. Int J Pharm. 2016;2(511):1130.

17. Capasso F, Leutner D. INT-012 The start of paedform–a pan-european paediatric formulary. British Medical Journal Publishing Group; 2018.

18. Taketomo CK, Hodding JH, Kraus DM. Pediatric & neonatal dosage handbook: an extensive resource for clinicians treating pediatric and neonatal patients. 23rd ed. Hudson, Ohio: Lexicomp; 2017.

19. BNF for Children (BNFC) 2016-2017: Royal Pharmaceutical Society of Great Britain, British Medical Association, Pharmaceutical Press; 2017.

20. Guy's and St. Thomas' King's College and University Lewisham Hospitals: Paediatric Formulary. 9th ed. Tomlin S, Kirk E, editors. UK: Guy's & St Thomas' NHS Foundation Trust; 2012.

21. Starkweather J, Moske AK. Multinomial logistic regression. 2011. http://www.unt.edu/rss/class/Jon/Benchmarks/MLR_JDS_Aug2011.pdf Assessed 4 March 2019.

22. Amidon GL, Lennernäs H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm Res. 1995;12(3):413-20.

23. Martir J, Flanagan T, Mann J, Fotaki N. Characterisation of the physicochemical properties of food and drinks used for the co-administration of drugs in the paediatric population. 2017. Abstract from AAPS annual meeting, San Diego, USA.

24. Kersten E, Barry A, Klein S. Physicochemical characterisation of fluids and soft foods frequently mixed with oral drug formulations prior to administration to children. Pharmazie. 2016;71(3):122-7.

25. Martir J, Flanagan T, Mann J, Fotaki N. Impact of co-administration of food and drink vehicles on the solubility of poorly soluble paediatric drugs. 2017. Abstract from AAPS annual meeting, San Diego, USA.

26. Martir J, Flanagan T, Mann J, Fotaki N. Effect of co-administration of foods and drinks on the dissolution of paediatric formulations – case study montelukast. 2018. Abstract from AAPS PharmSci 360, Washington DC, USA.

27. Martir J, Flanagan T, Mann J, Fotaki N. Effect of co-administration of foods and drinks on the dissolution of paediatric formulations – case study mesalazine. 2018. Abstract from AAPS PharmSci 360, Washington DC, USA.

28. Mistry P, Stirling H, Callens C, Hodson J, Batchelor H. Evaluation of patient-reported outcome measurements as a reliable tool to measure acceptability of the taste of paediatric medicines in an inpatient paediatric population. BMJ Open. 2018;8(7):e021961.

29. Committee for Medicinal Products for Human Use & Paediatric Committee. Guideline on pharmaceutical development of medicines for paediatric use EMA/CHMP/QWP/805880/2012 Rev. 2. 2013. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/07/WC500147002.pdf. Accessed 27 January 2016.

30. van der Vossen A. Paediatric formulations : pharmaceutical development and clinical evaluation [Ph.D. thesis]: Erasmus University Rotterdam; 2018.

31. Wells KA, Losin WG. In vitro stability, potency, and dissolution of duloxetine enteric-coated pellets after exposure to applesauce, apple juice, and chocolate pudding. Clin Ther. 2008;30(7):1300-8.

32. Carrier M-N, Garinot O, Vitzling C. Stability and compatibility of tegaserod from crushed tablets mixed in beverages and foods. American journal of health-system pharmacy. 2004;61(11):1135-42.

33. Manrique YJ, Lee DJ, Islam F, Nissen LM, Cichero JA, Stokes JR, et al. Crushed tablets: does the administration of food vehicles and thickened fluids to aid medication swallowing alter drug release? J Pharm Pharm Sci. 2014;17(2):207-19.

34. Mistry P, Batchelor H. Evidence of acceptability of oral paediatric medicines: a review. J Pharm Pharmacol. 2017;69(4):361-76.

35. Venables R, Batchelor H, Hodson J, Stirling H, Marriott J. Determination of formulation factors that affect oral medicines acceptability in a domiciliary paediatric population. Int J Pharm. 2015;480(1):55-62.

36. Phillips NM, Nay R. A systematic review of nursing administration of medication via enteral tubes in adults. J Clin Nurs. 2008;17(17):2257-65.

37. Zafar MU, Farkouh ME, Fuster V, Chesebro JH. Crushed clopidogrel administered via nasogastric tube has faster and greater absorption than oral whole tablets. J Interv Cardiol. 2009;22(4):385-9.

38. Martir J, Flanagan T, Mann J, Fotaki N. Stability of paediatric drugs co-administered with different foods and drinks. 2017. Abstract from AAPS annual meeting, San Diego, USA.

39. Russell R. Non-steroidal anti-inflammatory drugs and gastrointestinal damage—problems and solutions. Postgrad Med J. 2001;77(904):82-8.

40. Agostoni C, Buonocore G, Carnielli V, De Curtis M, Darmaun D, Decsi T, et al. Enteral nutrient supply for preterm infants: commentary from the European Society of Paediatric Gastroenterology, Hepatology and Nutrition Committee on Nutrition. J Pediatr Gastroenterol Nutr. 2010;50(1):85-91.

41. Batchelor H, European Paediatric Formulation I. Paediatric biopharmaceutics classification system: current status and future decisions. Int J Pharm. 2014;469(2):251-3.

42. Dresser GK, Bailey DG, Leake BF, Schwarz UI, Dawson PA, Freeman DJ, et al. Fruit juices inhibit organic anion transporting polypeptide–mediated drug uptake to decrease the oral availability of fexofenadine. Clin Pharmacol Ther. 2002;71(1):11-20.

43. Batchelor HK, Fotaki N, Klein S. Paediatric oral biopharmaceutics: key considerations and current challenges. Adv Drug Deliv Rev. 2014;73:102-26.

44. Food and Drug Administration. Providing information about pediatric uses of medical devices under section 515A of the Federal Food, Drug and Cosmetic Act. RockVille, MD; 2013.

Chapter 3: Assessing the impact of paediatric medicine co-administration with food and drinks on the solubility of poorly soluble drugs

Abstract

Objectives: Based on the recommended strategies for the oral administration of paediatric medicines with food and drink vehicles, the aims of this study were: (i.) to measure the physicochemical properties of a selection of (soft) food and drink vehicles, commonly reported to be mixed with paediatric medicines prior to administration; (ii.) to assess the impact of the co-administered vehicle on the solubility of two poorly soluble paediatric drugs. Montelukast (sodium) and mesalazine were selected as the model compounds.

Methods: 26 vehicles commonly used for paediatric medicine co-administration were selected; their physicochemical properties (pH, buffer capacity, surface tension, viscosity and osmolality) and macronutrient characteristics (sugar, protein and fat content) were measured/recorded. Solubility studies of two poorly soluble drugs were then performed in selected vehicles and in three USP buffers (pH 1.2, 4.5 and 6.8). Partial least square regression was performed to assess the impact of the physicochemical properties and content characteristics of the vehicles, as well as their interactions, on drug solubility.

Key findings: Distinguished differences were observed between the physicochemical properties and macronutrient composition of the different vehicles, not only among vehicle type but also within vehicles of the same subtype. Solubility studies of the two model compounds in selected drinks and soft foods, resulted in considerably different solubility values in each vehicle. Drug solubility was significantly affected by the vehicle physicochemical properties and macronutrient composition, with the solubility of montelukast being driven by vehicle pH, fat and protein content and the solubility of mesalazine by vehicle osmolality, viscosity and sugar content.

Conclusions: The observed vehicle-dependent impact on drug solubility could compromise its bioavailability, ultimately affecting the safety and/or efficacy of the drug and should be taken into consideration during paediatric product development.

1. Introduction

Paediatric formulation development has been affected by new regulations, additional funding opportunities and research initiatives in both the USA and Europe. Nevertheless, development of acceptable, age-appropriate dosage forms, whilst maintaining safety and efficacy and ensuring compliance, remains a challenge due to the unique requirements and limitations of this heterogeneous population (1, 2).

Healthcare professionals, parents and carers still face the need to manipulate medicines designed for adults in order to adapt dosage forms to give smaller doses, improve palatability and enhance compliance amongst paediatric patients (3). This manipulation can range from simple (*e.g.* tablet splitting) to more complex methods (*e.g.* tablet crushing for suspension preparation), and results in availability of patient-tailored medicines. A common practice is to mix medications with food or drink vehicles to mask the unsatisfactory palatability of a formulation, in cases that it cannot be improved through dosage form design, and/or to enhance acceptability through swallowing facilitation or texture improvement (4-6).

When this practice is intended, appropriate compatibility studies should be conducted in order to assess compatibility issues and evaluate the possible impact on drug bioavailability (7). Clear instructions on the type of vehicles appropriate for mixing with the medicine should be provided in the patient information leaflet (PIL), summary of product characteristics (SmPCs) and product labelling (7, 8). Similarly, appropriate warnings should be provided in cases that such practice is unsuitable, or has not yet been studied, with any mixing outside the recommendations being of the responsibility of the health care professional, patient, parent or carer (8).

In practice, the scientific rationale for co-administering a particular type of vehicle is often not evident (4). Most of the vehicles that appear in the paediatric dosing recommendations of SmPCs and PILs are chosen based on their taste and texture being child-friendly, and there is no general rule on how to administer oral medicines to the paediatric population in a safe and effective way (5, 9). Moreover, due to cultural differences in flavour preferences and accessibility of foods around the globe, different vehicles may be used to achieve adequate patient acceptability.

Carers often overlook the recommendations given in SmPCs and PILs, however, the clinical implications of this practice of medicine co-administration on drug behaviour and, subsequently, oral drug bioavailability are often not studied. Previous studies have shown that different foods or drinks can have dissimilar effects on the paediatric medicine *in vivo* performance due to their physicochemical properties. For example, the pH of pudding (pH 5.6), damaged the enteric coating of duloxetine pellets and affected its absorption compared to when the pellets were mixed with applesauce or apple juice (10); and the viscosity of applesauce, affected dissolution from warfarin crushed tablets in comparison to when these were mixed with orange juice (11).

In an effort to provide guidance on medicine co-administration, the FDA has recently launched a draft guidance entitled '*Use of liquids and/or soft foods as vehicles for drug administration: general considerations for selection and in vitro methods for product quality assessments*' (7). It is stated that the best vehicles to use for this clinical practice are those with relatively small fluctuations in their macronutrient composition and physicochemical characteristics, such as vehicle viscosity and pH. Furthermore, vehicle candidates should be screened concerning their interaction with drug/formulation and their adequacy to the target age group. This could guide an appropriate use of the vehicle and avoid possible clinical implications (7).

Knowledge of the composition and properties of the food and drinks will aid understanding of their in vivo impact on the drug product behaviour. Oral drug performance is influenced by drug bioavailability, which in turn is largely dependent on the drug available in the GI tract to undergo absorption (12). For poorly soluble compounds, oral drug absorption will be limited by drug solubility. Therefore, it is important to understand the impact of medicine co-administration with food and drinks on the behaviour of different drugs. The solubility of a drug serves as a surrogate indicator of oral biopharmaceutical performance and is one of the two factors that are used in the Biopharmaceutics Classification System (BCS) (13). It depends on the physicochemical properties of the drug and the composition of the dissolution medium the drug is exposed to; thus, it can be affected by the co-administered vehicle. To our knowledge, little attention has been devoted to

characterising soft foods and drinks commonly used in practice as well as identifying the impact of these properties on drug solubility.

The aims of the present study were: (i.) to measure the physicochemical properties of a number of food and drink vehicles that are commonly co-administered with paediatric medicines, and (ii.) to investigate the impact of the type of co-administered vehicle on the solubility of two poorly soluble paediatric drugs.

The characteristics of the model drugs to study were restricted to include a poorly soluble compounds, with pH-dependent solubility, documented usage in both children and adults, and recommended to be mixed with food or drink vehicles to facilitate administration in the paediatric population. Based on these criteria, montelukast (sodium) and mesalazine were selected.

Montelukast is a BCS class II compound with low aqueous solubility (0.2-0.5 µg/mL at 25 ^{o}C (14)), two pKas - 2.7 (strongest basic) and 5.8 (strongest acidic) (15), a clogP of 8.79 (16). The structure of montelukast sodium is shown in Figure 3.1. Instructions about the use of a paediatric montelukast formulation (Singulair® granules) report that the granules can be mixed with one teaspoonful of soft food (cold or at room temperature) (17).

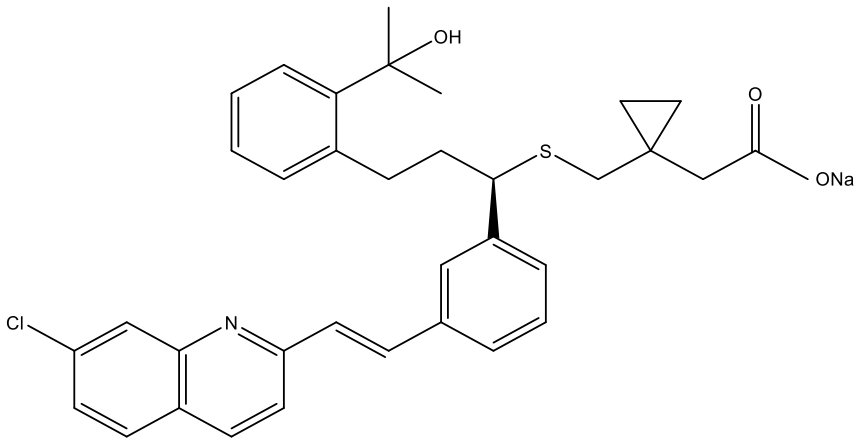


Figure 3.1. Structure of montelukast sodium (ChemDraw Professional 18.1)

Mesalazine has been classified as a BCS class IV drug, having an aqueous solubility of 0.84 mg/mL at 25^{o}C and a clogP of 0.98 (18). It is a zwitterion having a carboxyl

group (–COOH) with a pKa value of 2.3 and an amino group [($NH3^{+}$)−] with a pKa of 5.69 (19). The structure of mesalazine is shown in Figure 3.2. A commercially available mesalazine formulation (Pentasa® granules) is recommended to be mixed with juice or water to facilitate administration (17).

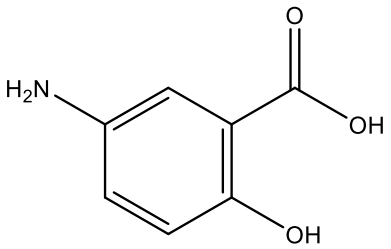


Figure 3.2. Structure of mesalazine (ChemDraw Professional 18.1)

2. Materials and methods

2.1 Materials

Ammonium acetate [High Performance Liquid Chromatography (HPLC) grade], 37 % hydrochloric acid, sodium hydroxide, sodium chloride, sodium acetate trihydrate, glacial acetic acid, sodium phosphate anhydrous, acetonitrile (HPLC grade) and methanol (HPLC grade) were purchased from Fisher Scientific (UK). Trifluoroacetic acid [TFA] (HPLC grade), montelukast sodium and mesalazine were obtained from Sigma-Aldrich Company Ltd. (UK). Water was ultra-pure (Milli-Q) laboratory grade.

Polytetrafluoroethylene [PTFE] filters (0.45 µm), RC filter papers (0.45 µm) (Whatman®, UK) and regenerated cellulose [RC] membrane filters (0.45 µm) (Cronus®, UK) were used.

Based on the recommendations gathered from the UK National (BNF-C (17)) and Hospital (20) formularies and taking into consideration the availability in a clinical setting, twenty-six different vehicles were selected and characterised. The origin, description, nutritional factors and manufacturer's preparation instructions of the vehicles studied are described in Table 3.1. Honey, jam, Coca-Cola as well as all squashes, milks, yoghurts, Bramley's applesauce (Bramley applesauce Colman's of

Norwich, UK) and juices were purchased from The Co-Operative (UK). Three infant formulas were used in the study: First Infant Milk (cow's milk-based formula) and Infasoy (soya-based formula) (Cow & Gate, UK), and Wysoy (soya-based formula) (SMA - Nestlé, UK). Vehicles with considerably different compositions available in different countries were also analysed. Mott's natural applesauce (Mott's LLP, USA) and Bauck Hof applesauce (Bauck Hof Apfelmark, Germany) were purchased from Amazon (UK) and were specifically chosen due to their different composition and region of origin.

Table 3.1. Identification, origin, nutritional facts and instructions for preparation (when applicable) of the vehicles studied. The vehicles, divided in two categories – soft foods and drinks, were further categorised into 9 subgroups.

Vehicles		Brand / Country	Energy (kJ / Kcal)	Nutrition (per 100mL or g)			Instructions for preparation
				Protein content (g)	Fat content (g)	Sugar content (g)	
Formula	Soya Wysoy	SMA (UK)	281 / 67	1.8	3.6	2.5	1 scoop of product for each 30 mL of water
	First milk	Cow & Gate First infant milk from newborn (UK)	257 / 60	1.3	3.4	7.3	
	Infasoy	Cow & Gate Infasoy (UK)	275 / 66	1.6	3.5	1.0	
Milk	Whole Fresh	The Co-Op (UK)	270 / 65	3.2	3.6	4.7	N/A
	Skimmed Fresh	The Co-Op (UK)	150 / 35	3.4	0.1	5.0	N/A
	Whole U.H.T	The Co-Op (UK)	280 / 70	3.3	4.0	4.7	N/A
	Soya	Alpro Soya (Belgium)	167 / 40	3.0	1.8	2.8	N/A
	Lactose free (*Semi-skimmed*)	Lactofree, Arla (Denmark)	160 / 40	3.6	1.5	3.0	N/A

Yoghurt	Plain	Yeo Valley (UK)	344 / 82	4.6	4.2	6.5	N/A
	Soya (*Alpro soya with yoghurt cultures*)	Alpro (UK)	212 / 50	4.0	2.3	2.1	N/A
	Lemon curd	Yeo Valley (UK)	536 / 127	4.7	4.4	16.9	N/A
	Double flavour (*Munch Bunch double Up Strawberry and Banana Yoghurt*)	Nestlé (Switzerland)	432 / 102	6.1	2.7	12.5	N/A
	Greek (*Greek recipe strained yoghurt total 0%)*	Fage (Greece)	243 / 57	10.3	0.0	4.0	N/A
	Liquid Strawberry (*Actimel for Kids*)	Danone (France)	312 / 74	3.3	1.3	11.2	N/A
	Strawberry Fromage (*Fromage Frais*)	Yoplait (USA)	399 / 95	5.3	2.3	9.9	N/A
Juice	Apple (*clear*)	The Co-Op (UK)	190 / 45	< 0.5	< 0.5	9.2	N/A
	Orange (*smooth*)	The Co-Op (UK)	180 / 42	0.5	< 0.5	9.2	N/A
Coca-Cola	Coca-Cola (*Original*)	The Coca-Cola company (UK)	180 / 42	0.0	0.0	10.6	N/A
Squash	Blackcurrant Ribena	Lucozade Ribena Suntory Ltd (UK)	183 / 43	0.0	0.0	10.0	50 mL of product diluted in 250 mL of water
	Blackcurrant Co-Op	The Co-Op (UK)	90 / 20	0.5	0.0	3.5	

	Orange	The Co-Op (UK)	60 / 15	0.2	0.0	1.7	25 mL of product diluted in 250 mL of water
Apple sauce	Bramley's UK	Bramley applesauce Colman's of Norwich (UK)	481 / 111	< 0.5	< 0.5	20.0	N/A
	Mott's Natural US	Mott's LLP (USA)	171 / 41	0.0	0.0	4.7	N/A
	Bauck Hof DE	Bauck Hof Apfelmark (Germany)	204 / 48	< 0.5	0.3	8.7	N/A
Honey	*Clear*	The Co-Op (UK)	270 / 65	0.1	0.2	80.8	N/A
Jam	Strawberry	The Co-Op (UK)	1064 / 251	< 0.5	< 0.5	49.0	N/A

(N/A: not applicable)

2.2 Methods

2.2.1 Preparation of vehicles and media

USP simulated gastric fluid sine pepsin (SGF*sp*) pH 1.2, acetate buffer pH 4.5 and phosphate buffer pH 6.8 were prepared following the USP 27 (21).

Prior to all analysis, squashes and formulas were prepared as per manufacturer's instructions (Table 3.1) and Coca-Cola was degassed. The dilution of the prepared squashes was not the same (blackcurrant: diluted 1/5 with water; orange: diluted 1/10 with water; Table 3.1). To evaluate if these differences in dilution had an effect on the physicochemical characteristics measured, confirmatory studies were performed with orange squash diluted on a 1/5 (concentrated squash/water) ratio. Results showed that the dilution of the squashes did not have a significant effect on the differences observed in the physicochemical properties measured (data not shown).

2.2.2 Physicochemical characterisation of the vehicles

Physicochemical characterisation of all vehicles included measurement of pH, buffer capacity, osmolality, surface tension and viscosity. All experiments were run in triplicate and results are expressed as mean values ± standard deviation (S.D.).

2.2.1.1 pH

The pH of each vehicle was measured, at room temperature, using a pH meter (Mettler Toledo S220 Seven Compact pH/Ion meter, Schwerzenbach, Switzerland). pH measurements took place immediately after opening the soft food/drink container or after vehicle preparation (in the cases of the formulas, squashes and Coca-Cola), and agitating the vehicle with a spatula for 5 s.

2.2.1.2 Buffer capacity

Buffer capacity was quantified by dropwise addition of 0.1 N sodium hydroxide or 0.1 N hydrochloric acid, measuring the volume required to change the pH by one unit, under constant agitation. Buffer capacity was then calculated using the following equation (Eq. 3.1) (22):

$$\frac{\mathrm{dB}}{\mathrm{dpH}} = \frac{\left(\begin{matrix}\text{cc. acid or base added}\\ \text{to cause pH change}\end{matrix}\right)\left(\begin{matrix}\text{normality factor}\\ \text{of acid or base}\end{matrix}\right)}{\left(\begin{matrix}\text{average volume of sample}\\ \text{over range involved}\end{matrix}\right)(\Delta pH)} \qquad \text{(Eq. 3.1)}$$

where $\frac{\mathrm{dB}}{\mathrm{dpH}}$ is the buffer capacity, $cc.$ is the concentration of acid or base added and ΔpH is the pH change produced.

2.2.1.3 Osmolality

Osmolality was measured via freezing-point depression method by a micro-osmometer (Advanced Instruments Inc. micro-osmometer Model 3300, Norwood, MA). 20 µl of sample were placed into the sampler, which was then inserted into the instrument's operating cradle, and subsequently lowered to the freezing chamber; this initiated the process of super cooling the sample. Following a solenoid-induced pulse and subsequent sample freezing, the liberated heat of fusion was related by a microprocessor to the sample's freezing point and osmolality was shown on a digital display (26).

The osmolality values of Bramley's applesauce (UK), honey and jam were quantified based on a set of appropriate dilutions of the vehicles in demineralised

water (% (w/w) vehicle/water). Concentration of vehicle (% (w/w)) and osmolality value measured were correlated, and the osmolality value of the undiluted vehicle (*i.e.* 100 % (w/w) vehicle/water) was calculated from the linear regression.

2.2.1.4 Surface tension

Surface tension was measured with the du Nouy ring method (23), using a ring tensiometer (Sigma 700 Force tensiometer, Attension, UK). 10 mL of sample were placed into a glass vessel (Ø = 46 mm) and temperature was set to 25 ^{o}C. The ring was submerged below the interface of the sample by moving the stage where the vessel was placed. After immersion, the stage was gradually decreased, and the ring pulled up the meniscus of the sample. The force required to raise the ring from the meniscus was measured and used to determine the surface tension.

2.2.1.5 Viscosity

Viscosity of the vehicles was determined using a rheometer (Bohlin Rheometer C-VOR, Malvern instruments, UK) fitted with a cone and plate geometry (4º cone angle, 40 mm diameter). Samples were added to the plate of the rheometer and analysis was carried out at 25^{o}C. Viscosity was measured at increasing shear stress (in the range of 0.1 to 4 Pa) for the drinks (modification of (24)) and increasing shear rate (from 0.1 to 85 s^{-1}) for the soft foods (modification of (25)), with 10 s delay time and 10 s integration time at each shear.

While the rheological curves for each sample were measured, for simplicity, the viscosity value used for statistical analysis was η50 (*i.e.* the measurement at a shear rate of 50 s^{-1}), which is the shear rate most often associated with swallowing (11).

2.2.3 Chromatographic conditions

Drug quantification was performed with HPLC with ultraviolet (UV) detection. Samples were analysed with an Agilent HPLC system 1100 series (montelukast) and 1200 series (mesalazine) (Agilent Technologies, USA). The HPLC method used for the analysis of montelukast is a modification of a published method by Raju KN *et al* (27). A revers ed-phase (RP) J.T. Baker Octadecyl-C_{18} column (250 mm x 4.6 mm, 5 µm particle size) was used. The mobile phase was composed of ammonium acetate buffer pH 5.6 and methanol (solvents A and B, respectively) delivered at a flow rate

of 1 mL min^{-1}. The selected gradient started with 10 % of solvent B, which was increased linearly to 50 % over 2 min, and linearly to 90 % between 2 and 4 min; at 11.30 min, the initial conditions of analysis were re-established. Injection volume was 100 µL. Analysis was performed at 20 ^{o}C and the detection wavelength was 284 nm. The HPLC method used for mesalazine analysis is a modification of a published method by Fadda H *et al* (18). A RP Agilent Eclipse XBD-C_{18} column (250 mm x 4.6 mm, 5 µm particle size) was used. The mobile phase was composed of methanol and 0.05 % TFA-Water (5:95) delivered at a flow rate of 1 mL min^{-1}. Injection volume was 20 µL. Analysis was performed at 40 ^{o}C and the detection wavelength was 304 nm.

The non-presence of a vehicle-matrix effect on drug detection, and HPLC analysis validity were confirmed by performing the following protocol: (i.) solution standards of the highest and lowest calibration curve concentrations were injected at least 3 times during each HPLC analysis run, and peak areas were analysed; and (ii.) 'blank' matrix standards were also injected, corresponding to vehicles exposed to the same conditions of the samples but containing no drug (after vehicle opening, and after placing vehicle into shaking water bath and collected at 4 and 24h) (data not shown).

2.2.4 Solubility studies

Solubility studies of montelukast and mesalazine were performed in sixteen food and drink vehicles; these included: formula (first milk), milk (whole U.H.T), yoghurts (plain flavour, lemon curd and Greek), juices (apple and orange), Coca-Cola, squashes (blackcurrant Ribena®, orange and blackcurrant Co-Op®), honey, jam and applesauces (Mott's natural applesauce US, Bramley's applesauce UK and Bauck Hof applesauce DE). Solubility studies of the two compounds were also performed in USP SGF*sp* pH 1.2, acetate buffer pH 4.5 and phosphate buffer pH 6.8 to compare between drug solubility in these media and in different food and drinks of corresponding pH and investigate the effect of media pH on the solubility of the compounds.

An excess amount of drug was added to 1.5 g of foods and 1.5 mL of buffers/drinks, in centrifuge tubes and stirred with a spatula for 30 s. A pilot study was performed to assess the impact of drug excess amount on drug solubility: different amounts of

drug were added to selected vehicles (*i.e.* formula, blackcurrant squash Ribena, Greek yoghurt, honey, applesauce DE and jam); results revealed no impact of the amount of drug used in the study on the solubility of the two compounds (data not shown). Capped tubes were placed in a shaking water bath (37 ^{o}C) (Grant SS40-2, Grant Instruments, UK), under constant shaking rate of 200 strokes/min, and protected from light to avoid photodegradation (28, 29). Samples were collected at 4 h and 24 h. Undissolved drug was removed by centrifugation (Eppendorf Heraeus Fresco 17 centrifuge, Thermo Electron LED GmbH, Germany) at 8000 rpm for 15 min, at 4 ^{o}C. 1000 µL of acetonitrile (montelukast) or 500 µL of 10 % (v/v) TFA/water (mesalazine) were then added to 500 µL (or mg) of the centrifuged sample. The mixture was vortexed for 1 min, and centrifuged. The supernatant was then filtered through a RC (montelukast) or PTFE (mesalazine) filter (0.45 µm), placed into amber HPLC vials and analysed. Honey and jam montelukast samples were diluted (dilution 1:2) with a solution of acetonitrile:water (1:1) prior to the treatment step.

Centrifugation technique was confirmed and validated as an efficient separation method of undissolved drug after three investigational studies were performed in selected vehicles (*i.e.* whole milk, orange juice, applesauce UK, plain yoghurt, Greek yoghurt). These were: (i.) filtration of saturated drink samples and comparison of drug solubility results with those obtained with centrifugation technique; (ii.) filtration of the supernatant after centrifugation of saturated samples and comparison with drug solubility results obtained when the supernatant was not filtered; (iii.) different centrifugation conditions (speed and time) and sequential centrifugations were tested and compared with drug solubility results obtained with original centrifugation conditions (data not shown).

All experiments were performed in triplicate. Quantification of the concentration of drug in samples was performed based on calibration curves. Fresh calibration curves (concentration range: 0.2 – 100 µg/mL (montelukast) and 5 – 200 µg/mL (mesalazine)) were prepared in the corresponding media (buffer or vehicle), by appropriate dilution of a 1000 µg/mL stock solution of the analytical standard in methanol (montelukast) or 0.05% TFA/water (mesalazine); the same treatment process was applied as described for the samples.

2.2.5 Data analysis

Vehicle characterisation data was analysed with one-way ANOVA using Statgraphics Centurion XVII software (Statpoint Technologies Inc, USA). Post hoc analysis was performed using Tukey Honest Significant Difference (HSD) test, in order to perform pairwise multiple comparison of between vehicles of the same subtype ($p < 0.05$ noting statistical significance).

Drug solubility results obtained in all studied vehicles were correlated to the physicochemical properties (pH, buffer capacity, surface tension, viscosity, osmolality) and macronutrient composition (percentage of fat, sugars and proteins) of the vehicles and selected interactions by partial least square regression (PLS-R) analysis using XLSTAT Software (an Add-In for Excel, Microsoft ®). The interactions selected as independent variables were (i.) interactions of vehicle pH with all other independent factors (physicochemical properties and macronutrient composition of the vehicles), chosen due to the difference between drug solubility in simple buffers and in vehicles of corresponding pH; and (ii.) interactions between vehicle viscosity and macronutrient composition, chosen due to the differences observed between drug solubility in the different soft foods.

PLS-R analysis is a statistical method which relates multivariate descriptor sets to different response sets (30). Four PLS-R models were constructed: one for the solubility of each drug at each time point studied (4 and 24 h). The quality of the models produced was assessed by R^2 and Q^2, which measure the fraction of the total variation of the response explained by the model and the fraction of the total variation of the response that can be predicted by the model, respectively. Q^2 and R^2 values above 0.5 and 0.8 refer to a model with good fit and prediction power, respectively (31). The statistical analysis generates components, based on the independent variables set to explain the response. These components are built iteratively so as to better explain the variability of the dependent variable (response), and their number is lower than the initial variables input into the model (30). The PLS-R models were built and evaluated based on full cross-validation (leave-one-out procedure). The number of principal components for each model was selected based on the optimum Q^2 value. The variable influence on projection (VIP) function, which describes the importance of the factors for the response cumulatively, was used to

identify which factors were most relevant for explaining drug solubility (with VIP > 1 noting statistical significance) (30). The standardised coefficients were used to indicate the relative impact (positive or negative) of each factor or interaction on drug solubility.

3. Results and discussion

3.1 Physicochemical characterisation of the food and drink vehicles

Results from the physicochemical characterisation (pH, buffer capacity, osmolality, surface tension and viscosity) of the twenty-six selected vehicles are shown in Figures 3.3 to 3.5.

3.1.1 pH

pH values measured were in the range of 3 to 4 for 'fruity' vehicles (*i.e.* squashes, juices, Coca-Cola, applesauce), pH range 4 to 4.5 for 'milky' soft foods (*i.e.* yoghurts) and pH range 6 to 7 for 'milky' drinks (*i.e.* milk, formulas) (Figure 3.3a).

As observed in the results, the pH of food and drinks of the same subtype is usually controlled within a specific range of pH, mostly due to their composition (32). For example, the pH of yoghurts in the range of 4 to 4.5 can be explained by the use of bacteria (normally, *lactobacillus acidophillus*) in their manufacturing process to convert milk sugar/lactose into lactic acid, which ultimately increases the acidity of the product (33). The pH of applesauces, orange and apple juice will be close to the pH of the corresponding fruits and may be more acidic depending on the presence of lemon juice in their composition (32). For example, the pH of the Mott's natural applesauce (US) was lower than the other applesauces due to this.

Differences in the pH of the vehicles used for medicine co-administration may affect the dissolution and absorption of drugs. For example, acidic vehicles such as yoghurts, applesauces, jam and honey (pH range 3 to 4.5), have been shown to compromise the chemical stability of acid sensitive drugs, especially in the case of manipulation of enteric coated dosage forms (34).

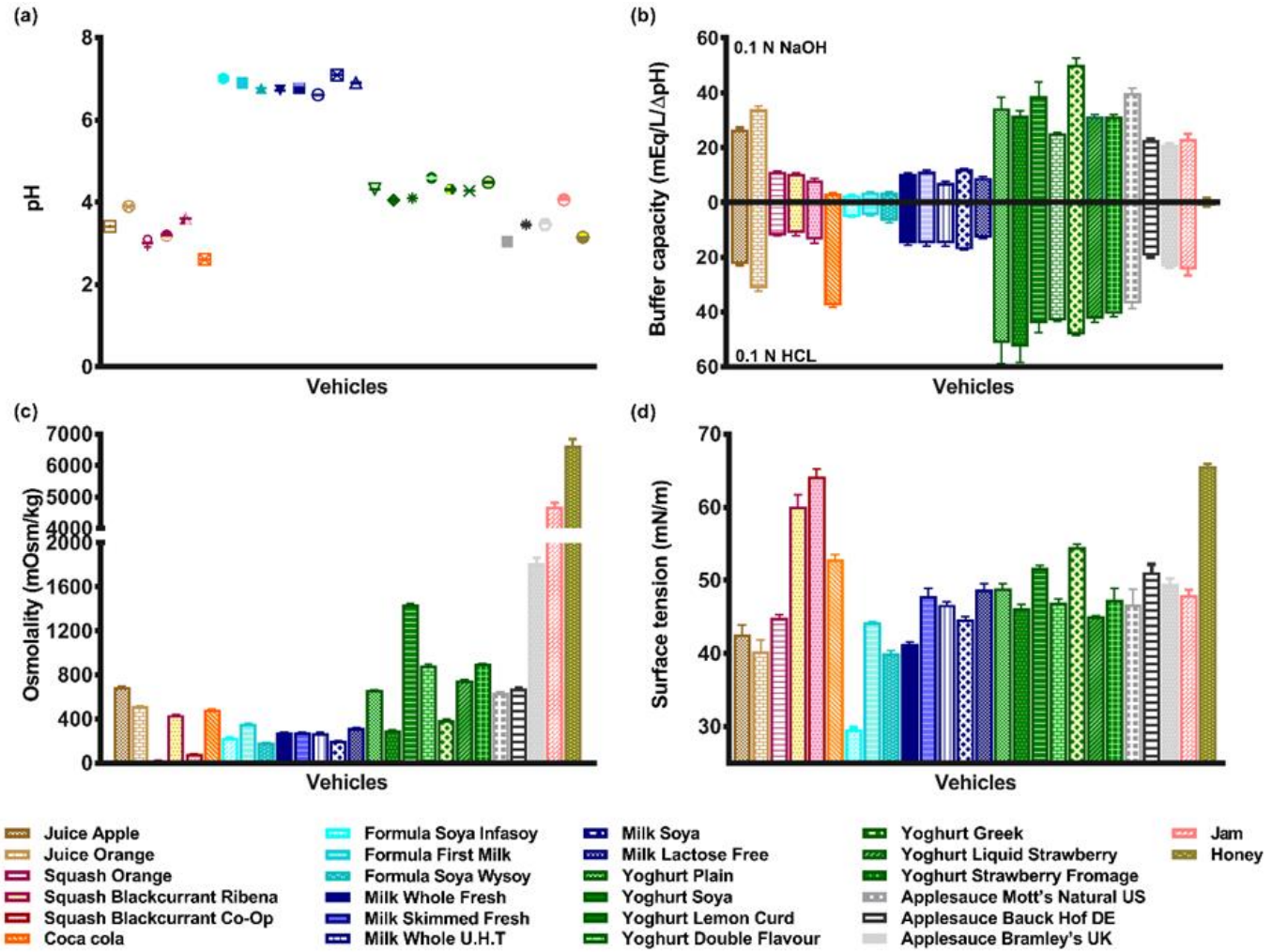


Figure 3.3. Physicochemical properties of 26 vehicles used for co-administration of drugs: (a) pH; (b) Buffer capacity, per addition of NaOH (upper part) or HCl (lower part); (c) Osmolality; (d) Surface tension. Each set of colours represents a subtype of vehicles.

3.1.2 Buffer capacity

Buffer capacity is higher in yoghurts, applesauces and jam, with lower values measured in formulas and orange squash (Figure 3.3b). Buffer capacity is especially important to the performance of ionisable compounds since a change in pH can affect the ionisation percentage of these drugs, and thus influence their solubility and dissolution (35). The different results obtained for the buffer capacity of these vehicles suggest that co-administration of a drug with the different vehicles may have an impact on its solubility.

3.1.3 Osmolality

The osmolality values of Bramley's applesauce UK, honey and jam could not be directly measured because they were above the maximum value measured by the micro-osmometer. Osmolality of these vehicles was obtained by extrapolation of the linear regression of the osmolality of a set of vehicle/water mixtures (% (w/w)) at various concentrations. Results are presented in Figure 3.4.

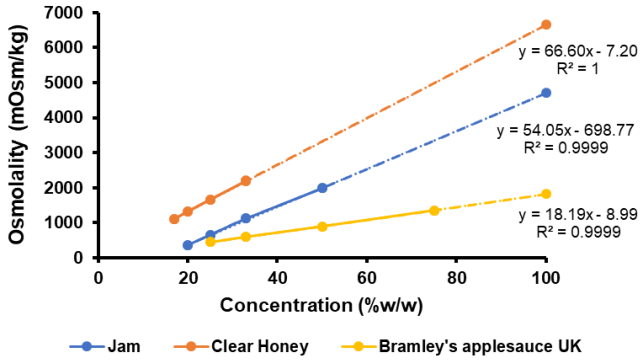


Figure 3.4. Linear regression of the osmolality values measured for the different mixtures vehicle (jam, honey and Bramley's applesauce US)/water (% (w/w)), which was used to extrapolate the osmolality value of the undiluted vehicles (dashed lines).

Osmolality of all tested vehicles is presented in Figure 3.3c. Osmolality was generally higher in soft foods than drinks, except for soya yoghurt (298.0 mOsm/kg), Greek yoghurt (393.0 mOsm/kg) and apple juice (693.3 mOsm/kg). The highest osmolality value was observed in honey (6650.0 mOsm/kg) and the lowest in orange squash (22.0 mOsm/kg). Significant differences were observed between vehicles of

the same subtype, namely between the different squashes and between the applesauces ($p < 0.05$). Osmolality of the orange squash was 4 and 20-fold lower than osmolality of the blackcurrant Co-Op and Ribena squashes, respectively. These differences can probably be attributed to the higher sugar content of the blackcurrant squashes in comparison to the orange squash (42).

The different osmolality values of the studied vehicles may affect the dissolution behaviour of a drug by inducing changes in the swelling behaviour of the formulation. When the difference in osmotic pressure between the inner and outer (GI environment) part of the formulation decreases, water penetration decreases as well, negatively affecting drug release (43).

3.1.4 Surface tension

Honey and blackcurrant squashes showed the highest surface tension, and soya formula the lowest (Figure 3.3d). The similar surface tension values measured for the dairy vehicles (except soya-derived products) can be related to the macronutrient composition of these vehicles. Dairy vehicles include surface-active constituents in their composition, such as fat, proteins and free fatty acids, which can affect the surface tension of these products (36). For the case of soya-derived products, these differ in composition from the other dairy vehicles due to the absence of milk protein and presence of soya protein, which has been shown to lower the surface tension (37). The surface tension of the juices and orange squash is lower in comparison to the other products due to the higher percentage of water in their composition and to the presence of fatty acids and their salts, which are surface active and reduce surface tension (38).

Differences were observed between the surface tension of Infasoy formula (30.0 mN/m) and the other formulas (40.1 mN/m (Wysoy) and 44.2 mN/m (first milk)) and between the surface tension of the squashes (orange squash 44.9 mN/m and blackcurrant Ribena and Co-Op squashes 60.1 and 64.2 mN/m, respectively).

The different surface tension values of the vehicles (including between vehicles of the same subtype) may impact the dissolution rate of a drug by influencing the wetting behaviour of the formulation (39).

3.1.5 Viscosity

The viscosity curves of the studied vehicles are shown in Figure 3.5. All drinks exhibited a Newtonian flow whereas the soft foods showed non-Newtonian flow (pseudoplastic behaviour), with the exception of honey. The soft foods studied contain milk and/or macromolecules (*i.e.* starch), which results in a significant increase in viscosity compared to that of the drinks ($p < 0.05$) (40).

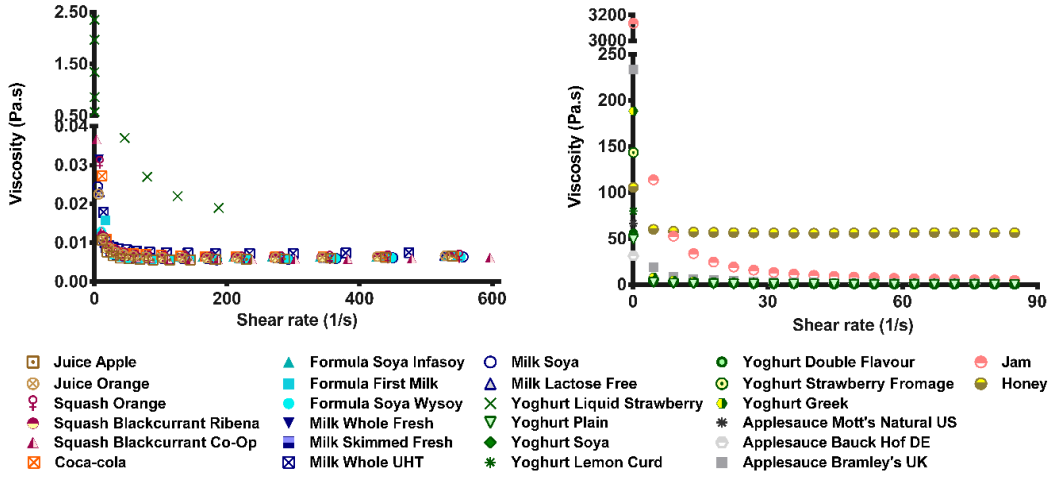


Figure 3.5. Viscosity of the drinks and soft foods measured at increasing shear stress (0.1 to 4 Pa) for the drinks and increasing shear rate (0.1 to 85 s^{-1}) for the foods (left and right panels, respectively) are shown in the left and right panels, respectively.

The clear differences in viscosity between the drinks and soft foods and between the different soft foods indicate that, depending on the child's diet, the overall absorption of certain drugs may be altered. For example, in infants whose diet consists mostly of liquids, the absorption of certain drugs may be increased due to the lower viscosity of the ingested food. Moreover, depending on the volume of vehicle administered, its viscosity can affect the pharmacokinetics of the drug due to alterations of physiological conditions (41). For example, mixing a medicine with a vehicle of higher viscosity such as jam may reduce the diffusion rate of the drug and therefore reduce its overall absorption (42).

3.2 Solubility studies of montelukast and mesalazine

Solubility of the two drugs differed in the vehicles studied (Figure 3.6). Solubility of montelukast in different USP buffers was shown to be pH-dependent (pH 1.2 < pH 4.5 < pH 6.8; Figure 3.7a), which is in accordance with previous reports (14). This is attributed to an increased solubilisation at more basic pHs, corresponding to the ionisation of the amino group of the compound (pKa 5.8) (15). Solubility of montelukast was generally lower in drinks than in soft foods, except the case of 'milky' drinks and Coca-Cola (Figure 3.4). In drinks, the lowest drug solubility was observed in apple juice (9 µg/mL; pH 3) and the highest in 'milky' drinks (pH 6.8), which is likely due to the pH effect on the solubility of montelukast. In soft foods, the lowest solubility of montelukast was measured in the plain yoghurt (1.6 mg/mL) and the highest in the Greek yoghurt (14.4 mg/mL). Interestingly, the solubility of montelukast in orange squash was 3 and 4-fold lower than in blackcurrant Ribena and Co-Op squashes, respectively, and in Mott's natural applesauce (US) drug solubility was around 2 to 3-fold lower than in the other applesauces ($p < 0.05$). Differences in drug solubility observed within vehicles of the same subtype and, therefore, same pH range (section 3.1.1), indicate that the solubility of montelukast is also driven by other vehicle physicochemical properties (pH, surface tension, osmolality, viscosity and buffer capacity) and macronutrient composition differences (percentage of sugars, fat and proteins). For example, both sugar content, and osmolality values vary within the different applesauces and squashes (sections 3.1.3).

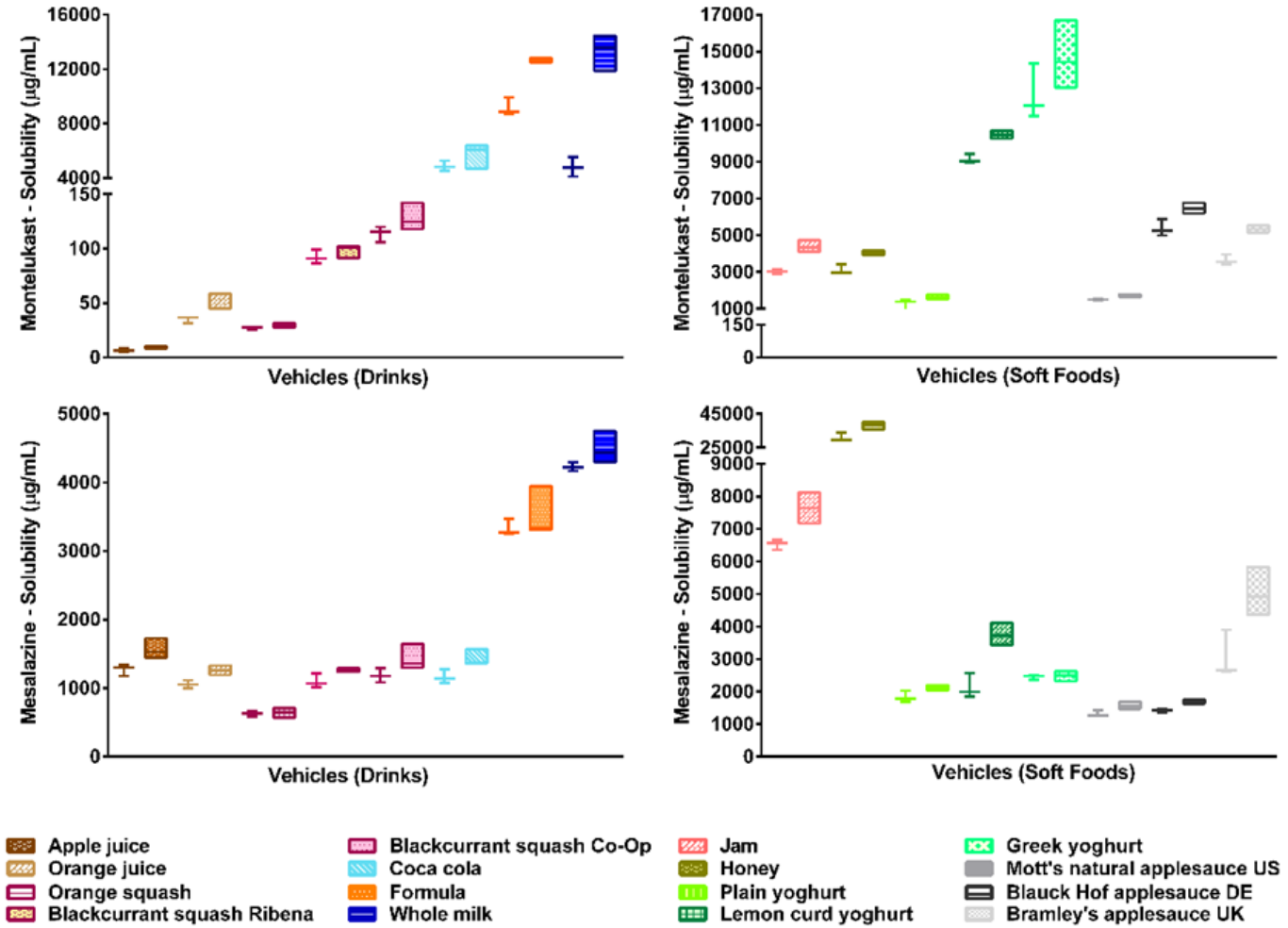


Figure 3.6. Solubility of montelukast and mesalazine (top and bottom sections, respectively) in the different drink and food vehicles, obtained after 4h (plot and whiskers) and 24h (floating bars); values shown represent the 3 replicates measured. Each set of colours represents a subtype of vehicles.

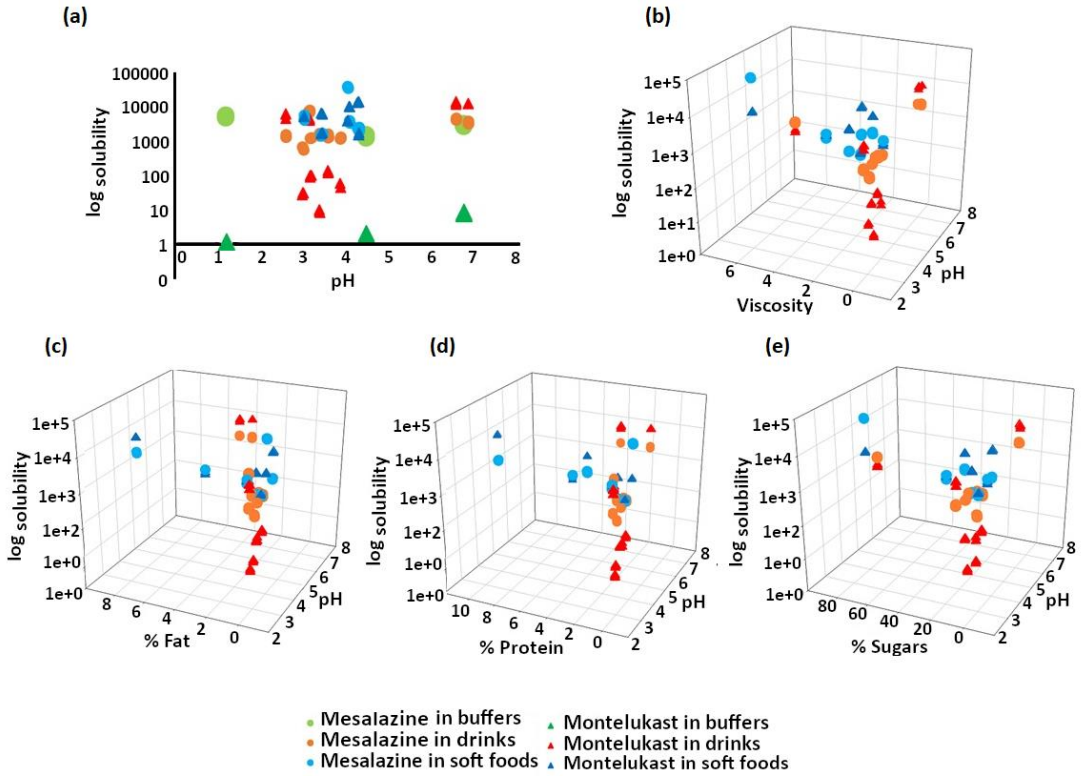


Figure 3.7. Solubility values (logarithmic scale) of montelukast and mesalazine in the selected media (soft foods, drinks) *vs* (a) pH (including solubility in buffers) (2D plot), and *vs* (b) pH and viscosity, (c) pH and % of fat, (d) pH and % of protein, and (e) pH and % of sugars (3D scatter plots).

For mesalazine, solubility was pH-dependent (solubility in pH 1.2 > solubility in pH 4.5 < solubility in pH 6.8; Figure 3.7a). A similar trend has been observed for the solubility of mesalazine in level I and II biorelevant media (44). Lower drug solubility at pH 4.5 could be attributed to the ionisation of this amino acid, which is the lowest at the isoelectric point (pI) of the compound (pH 4.3) and increases as the pH deviates from the pI (45, 46). A clear distinction between the solubility of mesalazine in drinks and soft foods could not be made (Figure 3.6). Drug solubility was lower in drinks with a pH ~ 4, probably due to the pH effect on drug ionisation and, consequently, solubilisation. Although trends could be seen between solubility and pH for the drinks, differences between drug solubility in drinks and soft foods of the same pH suggested that other vehicle properties, as well as differences in the macronutrient composition of the vehicles, influence drug solubilisation. For example, in yoghurts and applesauces (pH ~ 4), mesalazine exhibited a higher solubility than in drinks of same pH, which could relate to the higher viscosity of

these vehicles. For this drug, the highest solubility was obtained in honey (38.4 mg/mL) and the lowest in orange squash (0.63 mg/mL).

Overall, these results demonstrate that mixing these two poorly soluble drugs with soft foods and drinks significantly affects their solubility.

3D correlations of drug solubility values *vs* the vehicle composition (percentage of fat, sugar and protein)/viscosity and pH are presented in Figures 3.7b-3.7e. Analysis of the solubility of montelukast in the different vehicles revealed a crescent shaped trend between the pH and the percentages of fat and protein of the vehicles. The higher solubility of montelukast in the 'milky' products (milk, formula and yoghurts) in comparison to its solubility in the other vehicles might be related to the high lipophilicity (clogP = 8.79) and high affinity binding of this drug to proteins. This is in accordance with drug solubility studies previously conducted in milk which showed a positive relationship between drug lipophilicity, affinity binding to proteins and drug solubility in milk (47).

For mesalazine, a positive interplay was observed for vehicle pH, percentage of sugars and drug solubility in drinks and soft foods. In soft foods, it was possible to observe a positive correlation of drug solubility reliant on an increase of pH and viscosity. A positive correlation between drug solubility and media viscosity has been previously shown for similar compounds, which can justify the higher solubility of mesalazine in soft foods (*e.g.* honey, jam).

3.3 Statistical assessment of the vehicle-impact on drug solubilisation

PLS-R analysis was used to understand the vehicle-impact on the solubility of the two drugs. The variables and interactions of the PLS-R models constructed are presented in Figure 3.8. The PLS-R models developed for the solubility of montelukast at 4 and 24 h were defined by 4 and 5 components, respectively, had a good predictive power (Q^2 = 0.66 and 0.78, respectively) and showed a good fit to the experimental values (R^2 = 0.82 and 0.90, respectively). The pH and the percentage of fat and proteins were revealed as the factors with the most significant (positive) impact on the solubility of montelukast, while the buffer capacity of the

vehicles had a significant positive impact on the solubility of montelukast at 4 h but not at 24 h (Figure 3.8). Significant effects of the interaction of pH with buffer capacity and viscosity with fat (negative) and interaction of pH with osmolality, viscosity and fat, sugar and protein content (positive) were observed for this drug.

For mesalazine, the PLS-R models constructed for drug solubility at 4 and 24 h showed a good fit to the experimental values (R^2 = 0.98 and 0.94, respectively), a good prediction power (Q^2 = 0.95 and 0.91, respectively) and were defined by 3 and 2 components, respectively. Vehicle viscosity, osmolality and sugar content were the significant factors impacting the solubility of mesalazine (all positive effect), while significant effects from the interactions of viscosity with protein and fat content (negative) and the interaction of viscosity and sugar content (positive) were revealed (Figure 3.8).

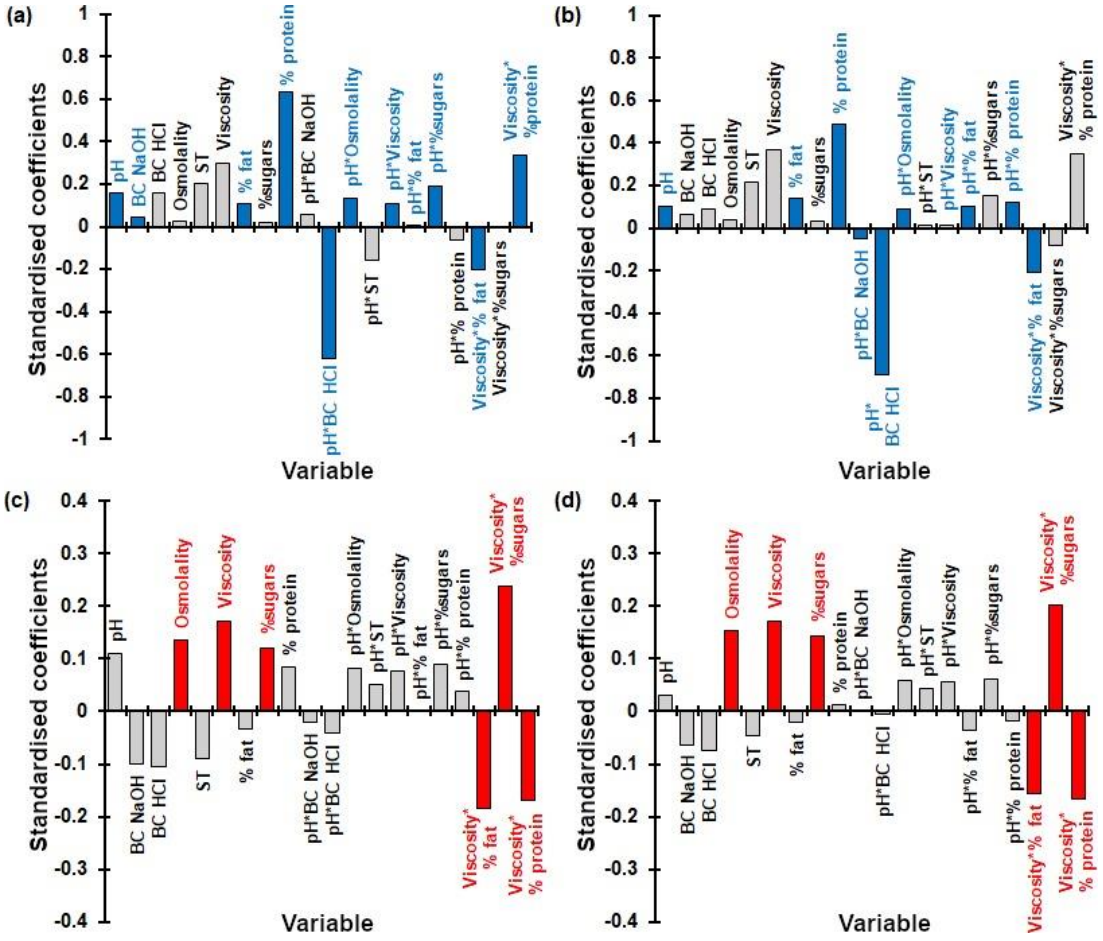


Figure 3.8. Standardised coefficients corresponding to the variables and interactions studies for the solubility of montelukast (a, b) and mesalazine (c, d), at 4 h (left panel; a, c) and 24 h (right panel; b, d). Blue and red colours denote coefficients with a significant impact on the

solubility of montelukast and mesalazine, respectively (VIP >1; data not shown). [BC = buffer capacity; ST = surface tension].

The difference in the vehicle variables (physicochemical properties and/or macronutrient composition) that impact the solubility of each drug suggest that the effect of the co-administered vehicle also depends on the properties of the drug (*e.g.* lipophilicity, pKa, acid/base properties). Knowledge of the physicochemical properties and macronutrient composition of the vehicles and drug/formulation physiochemistry could help predict the potential vehicle-impact on drug solubility and should be considered during compatibility assessments of the vehicle-drug product. For example, for drugs like montelukast, solubilisation may be increased when the formulation is mixed with a dairy vehicle than when mixed with juice. Moreover, the different results obtained for each drug highlight the importance of considering the nature of the vehicle utilised in common practice and possible effects of a change in recommendation. This is of particular importance considering that even though the recommendations for the administration of Singulair® granules (montelukast formulation) are to mix with '*a spoonful of cold soft foods*', differences in drug solubility were observed for soft foods of the same subtype (*e.g.* the solubilisation of montelukast will be 9-fold increased if mixed with the Greek yoghurt than if mixed with the plain yoghurt), demonstrating the potential risks of this practice. Moreover, the recommended vehicle to mix with Pentasa® granules (mesalazine formulation) is orange juice; however, if the juice is substituted for another vehicle such as formula, due to the child's diet/age, the medicine co-administration practice may result in a different drug solubilisation and, consequently, *in vivo* drug performance.

Ultimately, medicine co-administration with different vehicles may alter the clinical performance of a drug by affecting not only its solubility but also dissolution performance and, consequently, bioavailability. Although in some cases this can be beneficial, the risk of reduced efficacy and increased toxicity associated with this medicine administration practice is concerning.

4. Conclusions

Soft foods and drinks are commonly used to facilitate medicine administration to the paediatric population in order to improve palatability and enhance compliance.

In this study, twenty-six vehicles that are commonly mixed with oral medications to facilitate paediatric administration were characterised. Differences between the physicochemical properties of the different food and drink vehicles were observed, notably not only among vehicles, but also within vehicles of the same 'subtype'. These differences are expected to affect drug behaviour, such as its solubility and dissolution, especially in the case of a poorly soluble drug. Solubility studies of two model compounds, performed in selected drinks and soft foods resulted in considerably different solubility values in each vehicle. The solubility of the drugs was significantly affected by the vehicle physicochemical properties and characteristics, with the solubility of montelukast driven by pH and protein content and the solubility of mesalazine by viscosity, osmolality and vehicle sugar content. This vehicle-dependent impact on drug solubility could compromise drug bioavailability and should be taken into consideration during paediatric product development.

References

1. Turner MA, Catapano M, Hirschfeld S, Giaquinto C. Paediatric drug development: the impact of evolving regulations. Adv Drug Deliv Rev. 2014;73:2-13.

2. Ivanovska V, Rademaker CM, van Dijk L, Mantel-Teeuwisse AK. Pediatric drug formulations: a review of challenges and progress. Pediatrics. 2014;134(2):361-72.

3. World Health Organization. Development of paediatric medicines: points to consider in pharmaceutical development (Working document QAS/08.257/Rev.3). 2011. http://www.who.int/medicines/areas/quality_safety/quality_assurance/Rev3-PaediatricMedicinesDevelopment_QAS08-257Rev3_17082011.pdf. Accessed 21 January 2016.

4. Martir J, Flanagan T, Mann J, Fotaki N. Recommended strategies for the oral administration of paediatric medicines with food and drinks in the context of their biopharmaceutical properties: a review. J Pharm Pharmacol. 2017;69(4):384-97.

5. Akram G, Mullen AB. Paediatric nurses' knowledge and practice of mixing medication into foodstuff. Int J Pharm Pract. 2012;20(3):191-8.

6. Venables R, Stirling H, Batchelor H, Marriott J. Problems with oral formulations prescribed to children: a focus group study of healthcare professionals. Int J Clin Pharm. 2015;37(6):1057-67.

7. Food and Drug Administration. Center for Drug Evaluation and Research, Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments - Draft Guidance for Industry. 2018. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM614401.pdf. Accessed 6 October 2018.

8. Committee for Medicinal Products for Human Use & Paediatric Committee.: Guideline on pharmaceutical development of medicines for paediatric use EMA/CHMP/QWP/805880/2012 Rev. 2. 2013. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/07/WC500147002.pdf. Accessed 27 January 2016.

9. Belard S, Isaacs W, Black F, Bateman L, Madolo L, Munro J, et al. Treatment of childhood tuberculosis: caregivers' practices and perceptions in Cape Town, South Africa. Paediatr Int Child Health. 2015;35(1):24-8.

10. Wells KA, Losin WG. In vitro stability, potency, and dissolution of duloxetine enteric-coated pellets after exposure to applesauce, apple juice, and chocolate pudding. Clin Ther. 2008;30(7):1300-8.

11. Manrique YJ, Lee DJ, Islam F, Nissen LM, Cichero JA, Stokes JR, et al. Crushed tablets: does the administration of food vehicles and thickened fluids to aid medication swallowing alter drug release? J Pharm Pharm Sci. 2014;17(2):207-19.

12. Dressman J, Vertzoni M, Goumas K, Reppas C. Estimating drug solubility in the gastrointestinal tract. Advanced drug delivery reviews. 2007;59(7):591-602.

13. Amidon GL, Lennernäs H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm Res. 1995;12(3):413-20.

14. Okumu A, DiMaso M, Löbenberg R. Dynamic dissolution testing to establish in vitro/in vivo correlations for montelukast sodium, a poorly soluble drug. Pharm Res. 2008;25(12):2778-85.

15. Thibert R, Mach H, Clas S-D, Meisner DR, Vadas EB. Characterization of the self-association properties of a leukotriene D4 receptor antagonist, MK-0476. Int J Pharm. 1996;134(1-2):59-70.

16. Wishart DS, Knox C, Guo AC, Shrivastava S, Hassanali M, Stothard P, et al. DrugBank: a comprehensive resource for in silico drug discovery and exploration. Nucleic Acids Res. 2006;34(suppl 1):D668-D72.

17. BNF for Children (BNFC) 2016-2017: Royal Pharmaceutical Society of Great Britain, British Medical Association, Pharmaceutical Press; 2017.

18. Fadda H, Sousa T, Carlsson A, Abrahamsson B, Williams J, Kumar D, et al. Drug solubility in luminal fluids from different regions of the small and large intestine of humans. Mol Pharm. 2010;7(5):1527-32.

19. Allgayer H, Sonnenbichler J, Kruis W, Paumgartner G. Determination of the pK values of 5-aminosalicylic acid and N-acetylaminosalicylic acid and comparison of the pH dependent lipid-water partition coefficients of sulphasalazine and its metabolites. Arzneimittelforschung. 1984;35(9):1457-9.

20. Guy's and St. Thomas' King's College and University Lewisham Hospitals: Paediatric Formulary. 9th ed. Tomlin S, Kirk E, editors: Guy's & St Thomas' NHS Foundation Trust; 2012.

21. USP 30- NF 25. United States Pharmacopeia Convention. Rockville, USA; 2007.

22. Van Slyke DD. On the measurement of buffer values and on the relationship of buffer value to the dissociation constant of the buffer and the concentration and reaction of the buffer solution. J Biol Chem. 1922;52(525570):20.

23. du Nouy PL. A new apparatus for measuring surface tension. J Gen Physiol. 1919;1(5):521-4.

24. Oomah BD, Séry G, Godfrey DV, Beveridge TH. Rheology of sea buckthorn (Hippophae rhamnoides L.) juice. J Agric Food Chem. 1999;47(9):3546-50.

25. Akhtar M, Murray BS, Dickinson E. Perception of creaminess of model oil-in-water dairy emulsions: Influence of the shear-thinning nature of a viscosity-controlling hydrocolloid. Food Hydrocoll. 2006;20(6):839-47.

26. Koumantakis G, Wyndham L. An evaluation of osmolality measurement by freezing point depression using micro-amounts of sample. J Automat Chem. 1989;11(2):80-3.

27. Raju KN, Swamy TG, Rao AL. Development and validation of RP-HPLC method for the determination of montelukast sodium in bulk and in pharmaceutical formulation. J Pharm Chem Biol Sci. 2011;1(1):12-6.

28. Jensen J, Cornett C, Olsen CE, Tjørnelund J, Hansen SH. Identification of major degradation products of 5-aminosalicylic acid formed in aqueous solutions and in pharmaceuticals. Int J Pharm. 1992;88(1-3):177-87.

29. Smith GA, Rawls CM, Kunka RL. An automated method for the determination of montelukast in human plasma using dual-column HPLC analysis and peak height summation of the parent compound and its photodegradation product. Pharm Res. 2004;21(9):1539-44.

30. Wold S, Sjöström M, Eriksson L. PLS-regression: a basic tool of chemometrics. Chemom Intell Lab Syst. 2001;58(2):109-30.

31. Lundstedt T, Seifert E, Abramo L, Thelin B, Nyström Å, Pettersen J, et al. Experimental design and optimization. Chemom Intell Lab Syst. 1998;42(1):3-40.

32. Cunningham E. What impact does pH have on food and nutrition? J Acad Nutr Diet. 2009;109(10):1816.

33. Arioui F, Ait Saada D, Cheriguene A. Physicochemical and sensory quality of yogurt incorporated with pectin from peel of Citrus sinensis. Food Sci Nutr. 2016;5(2):358-64.

34. Carrier M, Garinot O, Vitzling C. Stability and compatibility of tegaserod from crushed tablets mixed in beverages and foods. Am J Health Syst Pharm. 2004;61(11).

35. Mooney K, Mintun M, Himmelstein K, Stella V. Dissolution kinetics of carboxylic acids II: Effect of buffers. J Pharm Sci. 1981;70(1):22-32.

36. Whitnah C. The surface tension of milk. A review. J Dairy Sci 1959;42(9):1437-49.

37. Shao YY, Lin KH, Kao YJ. Modification of foaming properties of commercial soy protein isolates and concentrates by heat treatments. J Food Qual. 2016;39(6):695-706.

38. Del Castillo ML, Dobson G, Brennan R, Gordon S. Fatty acid content and juice characteristics in black currant (Ribes nigrum L.) genotypes. J Agric Food Chem. 2004;52(4):948-52.

39. Smith BT. Solubility and dissolution. Remington Education: Physical Pharmacy. 1st ed. UK: Pharmaceutical Press; 2015. p. 31-50.

40. Klein S, Dressman JB, Butler J, Hempenstall JM, Reppas C. Media to simulate the postprandial stomach I. Matching the physicochemical characteristics of standard breakfasts. J Pharm Pharmacol. 2004;56(5):605-10.

41. Shimoyama Y, Kusano M, Kawamura O, Zai H, Kuribayashi S, Higuchi T, et al. High-viscosity liquid meal accelerates gastric emptying. J Neurogastroenterol Motil. 2007;19(11):879-86.

42. Batchelor H. Influence of Food on Paediatric Gastrointestinal Drug Absorption Following Oral Administration: A Review. Children. 2015;2(2):244-71.

43. Rudolph MW, Klein S, Beckert TE, Petereit HU, Dressman JB. A new 5-aminosalicylic acid multi-unit dosage form for the therapy of ulcerative colitis. Eur J Pharm Biopharm. 2001;51(3):183-90.

44. Andreas CJ, Chen Y-C, Markopoulos C, Reppas C, Dressman J. In vitro biorelevant models for evaluating modified release mesalamine products to forecast the effect of formulation and meal intake on drug release. Eur J Pharm Biopharm. 2015;97:39-50.

45. Déo SC, Andreazza IF, Possamai JC. Development of mesalazine pellets coated with methacrylic-derived polymer. Braz J Pharm Sci. 2011;47(1):103-9.

46. Tseng HC, Lee CY, Weng WL, Shiah IM. Solubilities of amino acids in water at various pH values under 298.15 K. Fluid Phase Equilib. 2009;285(1):90-5.

47. Macheras PE, Koupparis MA, Antimisiaris SG. Drug binding and solubility in milk. J Pharm Res. 1990;7(5):537-41.

Chapter 4: Evaluating the effect of co-administration with food and drinks on the dissolution of paediatric formulations – a case study of montelukast sodium and mesalazine

Abstract

Objectives: The aim of this study was to use *in vitro* dissolution testing, under infant simulating conditions, to evaluate the effect of co-administration with vehicles on the dissolution performance of two poorly soluble paediatric drugs.

Methods: Dissolution studies of mesalazine and montelukast formulations were conducted with mini-paddle apparatus on a two-stage approach: simulated gastric fluid without enzymes followed by simulated intestinal fluid. The testing scenarios were designed to reflect daily administration practices: (i.) direct administration of formulation; (ii.) formulation co-administered with food and drinks, immediately after mixing; and 4 h after mixing (iii.).

Key findings: Drug dissolution was significantly affected by medicine co-administration with vehicles, compared to the scenario of direct administration of formulation with a standard glass of water. Differences were observed on drug dissolution when the formulations were mixed with different vehicles of the same subtype. The time between preparation and testing of the drug-vehicle mixture also had an impact on drug dissolution behaviour. Drug dissolution was shown to be significantly affected by the physicochemical properties and composition of the vehicles, drug solubility in each vehicle and drug/formulation characteristics.

Conclusions: It is essential to consider the nature of the vehicles commonly used for paediatric drug administration and the possible vehicle-effects on drug product performance. Age-appropriate *in vitro* dissolution testing is a useful biopharmaceutical tool for estimating drug dissolution in conditions relevant to the paediatric population and evaluate the impact of medicine co-administration with vehicles on paediatric formulation performance.

1. Introduction

Paediatric oral drug development and administration remains challenging due to specific age-related problems. Availability of authorised, age-appropriate medicines is limited and there is no general rule of how to safely administer oral medicines to the paediatric population (1, 2). Therefore, pharmacists and carers often manipulate adult dosage forms prior to administration.

The use of food and drinks as vehicles for medicine co-administration is common practice to deliver a specific dose and improve compliance, yet the scientific rationale for selecting a particular type of vehicle for mixing with the medicine is often not evident (3-5). The majority of vehicles suggested for medicine co-administration seem to be recommended more on the basis of their taste and texture for the paediatric population rather than their impact on *in vivo* drug product performance. In addition to the possible negative effects on dose accuracy (as often reported (5-7)), drug manipulation and mixing with different food and drinks can also affect drug stability, solubility and bioavailability, ultimately leading to either sub-therapeutic or toxic drug levels (8-10). These effects are still often unaddressed.

It has been shown that different food and drinks can have an effect on paediatric medicine performance. For instance, the solubility of two poorly soluble compounds (montelukast and mesalazine) commonly administered to children was significantly affected by the physicochemical properties (pH, buffer capacity, surface tension, osmolality, viscosity) and macronutrient composition (fat, sugar and protein content) of commonly used vehicles (11). Similarly, medicine co-administration with different vehicles may affect drug dissolution properties to a different extent. Dissolution of amlodipine (BCS class I; weak base, pKa 8.6; logP 3.0 (12)) from crushed tablets mixed with jam has been shown to be slower in comparison with mixing with other vehicles (yoghurt, honey, orange juice and water) (13). Dissolution studies of crushed warfarin (BCS class I; weak acid, pKa 5.1; logP 2.7 (14, 15)) and carbamazepine (BCS class II; neutral compound; logP 2.5 (15, 16)) tablets mixed with water or orange juice resulted in a faster drug dissolution in comparison to direct administration of whole tablets. In comparison, no differences were observed between drug dissolution from crushed tablets mixed with honey, jam or yoghurt and the direct introduction of tablets scenario (13). Compatibility studies

of tegaserod (BCS class II; weak base, pKa 9.8; logP 2.6 (15, 17)), from crushed tablets in food/drinks (water, apple juice, orange juice, and applesauce), revealed that while the drug was compatible with the vehicles, the dissolution profiles of the crushed tablets mixed with orange juice and applesauce were not comparable with those of intact tablets (18). The time between preparation and administration of the mixture may also have an effect on drug solubility, drug stability, and consequently oral drug absorption (10). This vehicle-impact might be critical for certain medications (*e.g.* when immediate release is needed for a fast-therapeutic action), since food-drug interactions can have a significant impact on drug bioavailability and, consequently, therapeutic efficacy (19, 20).

Recently, the FDA issued a draft guidance addressing the recommended approaches for determination of the suitability of the vehicles intended for co-administration of paediatric medicines (21). Guidance is given on vehicle selection, description of standardised *in vitro* methods for evaluating vehicle compatibility, and suggestions on product labelling for communication of acceptability of vehicles (21). It is necessary to conduct these investigations in order to fully understand the impact of this practice on drug formulation behaviour and better guide healthcare practitioners, patients and carers regarding medicine co-administration with vehicles, in the paediatric population.

In vitro dissolution testing is a widely used *in vitro* tool for drug product performance characterisation. Dissolution tests are used for several applications including: assessment of batch-to-batch quality process control and quality assurance, formulation development, identification of food effects in the dissolution and bioavailability of orally administered drugs, and of drug solubility limitations and stability issues (22, 23). Dissolution tests have been shown to predict *in vivo* drug behaviour in adults by addressing both medicine administration practices and the physiological gastrointestinal (GI) conditions that can affect drug dissolution (22, 24). However, these tests are unsuitable for assessing drug performance in paediatrics. The use of dissolution tests to study the impact of medicine co-administration with vehicles on paediatric drug performance would require the incorporation of age-specific gastrointestinal (GI) tract parameters (namely, pH, media volumes and composition and different dosing scenarios) (25).

The aims of this study were two-fold: (i.) to evaluate the effect of the co-administration with vehicles on the dissolution performance of formulations of two poorly soluble compounds; and (ii.) to evaluate the effect of different administration practices (*i.e.* time between preparation and administration of the mixture formulation-vehicle) on drug dissolution. Drug dissolution studies were conducted with mini-paddle apparatus under relevant conditions (*e.g.* pH, fluid volumes and transit times). Montelukast and mesalazine were selected as model compounds; two formulations of each drug were studied (montelukast: Singulair® granules and Actavis® chewable tablets; mesalazine: Pentasa® and Salofalk® granules).

2. Materials and methods

2.1 Materials

Ammonium acetate [High Performance Liquid Chromatography (HPLC) grade], 37% hydrochloric acid, sodium hydroxide, sodium chloride, glacial acetic acid, potassium dihydrogen phosphate, acetonitrile (HPLC grade) and methanol (HPLC grade) were purchased from Fisher Scientific (UK). Trifluoroacetic acid [TFA] (HPLC grade), montelukast sodium (pharmaceutical secondary standard) and mesalazine (≥ 99 %) were obtained from Sigma-Aldrich Company Ltd (UK). Water was ultra-pure (Milli-Q) laboratory grade. Regenerated cellulose [RC] membrane filters (0.45 µm) (Cronus®, UK), and filter papers (0.45 µm), polytetrafluoroethylene [PTFE] filters (0.45 µm), and glass microfiber [GF/D] filters (2.7 µm) (Whatman®, UK) were used. Porous full flow polyethylene cannula filters (10 µm) were obtained from Quality Lab Accessories LCC (USA). Nine different soft foods and drinks were used as co-administration vehicles. They were chosen based on differences in their composition, physicochemical properties, and drug solubility in each vehicle (Chapter 3)(11, 26). Orange squash, milk U.H.T. full fat, and orange juice (smooth) were from The Co-Operative (UK). Blackcurrant squash was from Lucozade Ribena Suntory Ltd (UK). First Infant Milk (cow's milk-based formula) was from Cow & Gate (UK). Applesauces were Bramley applesauce Colman's of Norwich (referred to as 'applesauce UK') from Unilever (UK), and Apfelmark applesauce (referred to as 'applesauce DE') from Bauck Hof (Germany). Plain yoghurt from Yeo Valley (UK) and Greek yoghurt from Fage (Greece) were also used. The four formulations

studied were kindly donated by AstraZeneca (UK). Product information is summarised in Table 4.1.

Table 4.1. Information of the formulations used in this study.

Active principal ingredient (API)	Brand	Manufacturer	Formulation type/ release mechanism	Dose tested	Administration recommendations (27)
Mesalazine	Salofalk®	Dr. Falk Pharma (UK)	Granules / Delayed release pH-dependent	135 mg	Granules should be placed on tongue and washed down with water without chewing.
	Pentasa®	Ferring (UK)	Granules / Extended release pH-independent coating	135 mg	Granules should be placed on tongue and washed down with water or orange juice, without chewing. Contents of one sachet should be weighed and divided immediately before use; any remaining granules should be discarded.
Montelukast	Singulair®	Merck Sharp & Dohme Ltd (UK)	Granules / Immediate release	4 mg	Granules may be swallowed or mixed with cold, soft foods (not liquid), and taken immediately.
	Actavis®	Actavis (UK)	Chewable tablets / Immediate release	5 mg	Tablet should not be taken with food; should be taken at least one hour before or two hours after food.

2.2 Methods

2.2.1 Dissolution media preparation

Simulated gastric fluid *sine pepsin* (SGF*sp*) pH 1.2 and simulated intestinal fluid (SIF*sp*) were prepared according to the USP recipes (28). Double concentrated SIF*sp* containing an additional amount of sodium hydroxide (to neutralize the acid present on the first step) was prepared for the two-stage dissolution studies performed.

2.2.2 Sample preparation

Squashes and formula were prepared as per manufacturer's instructions (formula: 1 scoop of powder (approximately 4.5 g) was added to 30 mL of boiled cooled water; squashes: 25 (orange) or 50 (blackcurrant) mL of concentrated product were diluted in 250 mL of water).

For the direct administration scenario, the formulations were introduced in the media without being mixed with a vehicle. For the scenario of mixing the formulations with vehicles, each sample was prepared by addition of the formulations (corresponding to the 'dose tested' in Table 4.1) to 25 mL of drink or 10 mL (approximately 10 g) of soft food, at room temperature. All samples were manually mixed with a stainless-steel spatula, for 30 s, and tested within 5 min of preparation. Actavis® chewable tablets were crushed with a spatula prior to being mixed with the vehicles or tested.

To test different administration practices, samples with vehicles were prepared as described above and set aside (at room temperature and protected from direct light) and after 4 h they were remixed with a stainless-steel spatula, prior to performing the study.

2.2.3 *In vitro* dissolution studies

Dissolution studies were performed with a mini-paddle apparatus (Agilent Technologies 708-DS apparatus configured with TruAlign 200 mL vessels and electropolished stainless steel mini-paddles; Agilent, USA). Experiments were conducted in a two-stage approach: in SGF*sp* pH 1.2 (total volume with sample: 100 mL), for 1 h, followed by SIF*sp* pH 6.8 (final volume: 200 mL), for 3 h. A dissolution study with a sequential media change mimics the passage of oral dosage forms through the GI tract, providing an understanding of the *in vivo* drug performance (29). Experiments were conducted at 37 ± 0.5 ^{o}C and the agitation rate of the mini-paddle was set to 50 revolutions per minute (rpm). Sample collection took place at 5, 15, 30, 45, 60, 75, 90, 120, 180 and 240 min. 2 mL samples were withdrawn (with volume replacement with the corresponding media), using a 2 mL glass syringe (Fortuna Optima® fitted with a stainless tubing) through a cannula fitted with a full flow filter (10 µm). All experiments were performed without direct

light exposure to avoid photodegradation of the drugs (30, 31). After collection, samples were filtered through a GF/D filter (2.7 µm) and treated. Sample treatment was as follows: 1000 µL of acetonitrile (montelukast) or 10 % (v/v) TFA/water (mesalazine) were added to 500 µL of sample. This mixture was vortexed (HTZ, UK) for 1 min and centrifuged (8000 rpm, 15 min, 4 ^{o}C) (Beckman Coulter J2-MC centrifuge, UK). The supernatant was filtered through a RC (montelukast) or PTFE (mesalazine) filter (0.45 µm), placed in an HPLC amber vial and analysed. The pH of the media was measured at the end of each experiment.

The effect of different administration scenarios and testing conditions was investigated by varying the dissolution test parameters, as described in Table 4.2. These were: (1) effect of co-administration of formulation with selected vehicles in comparison to direct administration of formulation; (2) effect of different mixing patterns (*i.e.* time between preparation and administration/testing of the formulation-vehicle mixture); and (3) effect of hydrodynamics (50 *vs* 100 rpm, in selected studies of Pentasa® and Singulair® granules).

All experiments were performed in triplicate. Fresh calibration curves (concentration range: 0.5 – 100 µg/mL (montelukast) and 0.5 – 200 µg/mL (mesalazine)) were prepared in the corresponding media, by appropriate dilution of a 1000 µg/mL stock solution of the analytical standard in methanol (montelukast) or 0.05 % TFA/water (mesalazine); the same treatment process was applied as described for the samples. Results were expressed as mean % drug dissolved ± standard deviation (S.D.), at the given sampling time.

Table 4.2. Administration scenarios and testing conditions investigated.

Setup	Agitation speed (rpm)	Scenario: direct administration	Scenario: mixing with vehicles	Formulations	Mixing pattern (h)
1	50	✓	M, OJ, BLS, PY, $APS_{UK,}$ F, OS, GY, APS_{DE}	All	0
2	50	N/A	M, OJ, BLS, PY, APS_{UK}	All	4
3	100	✓	M, OJ, BLS, PY, APS_{UK}	Singulair®, Pentasa®	0

(BLS = blackcurrant squash; OS = orange squash; M = milk; F = formula; OJ = orange juice; PY = plain yoghurt; GY = Greek yoghurt; APS_{UK} = applesauce UK; APS_{DE} = applesauce DE; N/A = not applicable)

2.2.4 Chromatographic conditions for drug analysis

The chromatographic methods used for drug analysis were modifications of published methods (32, 33). Drug quantification was performed with HPLC with ultraviolet (UV) detection (Agilent HPLC system 1100/1200 series; Agilent, USA). A RP Agilent Eclipse XDB C_{18} column (250 mm x 4.6 mm, 5 µm particle size) was used for both drugs. For montelukast, the mobile phase was composed of ammonium acetate buffer pH 5.5 and methanol (solvents A and B, respectively) delivered at a flow rate of 1 mL min^{-1}, on a linear gradient. The selected gradient started with 10 % of solvent B, which was increased to 50 % within 2 min, and 90 % within 4 min; at 11.30 min, the initial conditions of analysis were re-established. Injection volume was 100 µL. Analysis was performed at 20 ^{o}C and the detection wavelength was 284 nm. Elution time for montelukast was 8.9 min. For analysis of mesalazine, the mobile phase was composed of 0.05 % TFA/water and methanol (95:5), delivered at a flow rate of 1 mL min^{-1}. Injection volume was 20 µL. Analysis was performed at 40 ^{o}C and the detection wavelength was 304 nm. Elution time for mesalazine was 4.6 min.

2.2.5 Statistical analysis of dissolution data

To describe and compare the dissolution profiles obtained, linear trapezoidal method was used to calculate the area under the curve of each profile over 4 h ($AUC_{0\text{-}4h}$). This allowed the use of one value representative of drug dissolution to compare the different scenarios tested.

One-way analysis of variance (ANOVA) with a post-hoc Tukey Honest Significant Difference (HSD) test was conducted to investigate statistically significant differences ($p < 0.05$ noting significance level) in the $AUC_{0\text{-}4h}$ between direct administration of formulation and mixing the formulations with the different vehicles. T-test analysis was used to compare $AUC_{0\text{-}4h}$ results obtained between drug dissolution after mixing the formulations with vehicles of same subtype or drug dissolution after mixing the formulations with the same vehicle under different testing conditions (*i.e.* agitation rate or time between preparation and mixing) ($p < 0.05$ noting significance). The analyses were performed with GraphPad Prism® v.7 software (San Diego, USA).

Partial least squares regression (PLS-R) analysis was used to correlate the $AUC_{0\text{-}4h}$ values of the different testing scenarios (response factor) with the physicochemical properties and macronutrient composition of the vehicles (pH, buffer capacity, surface tension, viscosity, osmolality; percentage of fat, sugars and proteins), drug solubility in each vehicle, type of formulation and testing conditions (*i.e.* preparation time) (XLSTAT Software; an Add-In for Excel, Microsoft®). When analysing both drugs together, drug characteristics (logP [log octanol-water partition coefficient] and ionisation % [obtained from ACD/Labs© 2010-2018]) were also considered as variables. The quality of the model was evaluated with the square of the coefficient of determination (R^2) and goodness of prediction (Q^2), with values close to 1 being indicative of good fit and prediction power, respectively (34). Full cross-validation (leave-one-out procedure) was used to develop and evaluate the regression model. The optimum number of calibration factors for each model was selected based on the optimum predictability of the model and predicted residual error sum of squares (PRESS). The standardised coefficients of the factors indicated the relative effect (positive or negative) of their corresponding variables on the response. The variable importance in projection (VIP) value was used to evaluate the importance of each factor on the model (34). Model variables with VIP values > 1 were evaluated as the most important in explaining the variation in the dependent variable, while values between 0.7 and 1 were considered moderately influential for the model. Values < 0.7 were deemed not of significance for the prediction of the dependent variable (34).

3. Results and discussion

3.1 Effect of medicine co-administration with food and drinks on drug dissolution

Dissolution of montelukast from the two formulations revealed a significant effect of medicine co-administration with food and drink vehicles, compared to the direct administration scenario (Figures 4.1 and 4.2). For Singulair® granules, the $AUC_{0\text{-}4h}$ was significantly lower for the direct administration scenario in comparison to when the granules were mixed with vehicles, except for orange juice, blackcurrant squash and applesauce UK. For the co-administration with drinks scenario, drug dissolution

was higher at 4 h when the formulation was mixed with milk (61.9 %), followed by when it was mixed with formula, orange squash, blackcurrant squash and orange juice (% drug dissolved = 41.1, 16.7, 10.8, and 7.7, respectively). For an ionisable compound like montelukast (amphoteric; pKa_{basic} 2.7 and pKa_{acidic} 5.8 (35)) an increase in pH can affect the ionisation % of the drug. Therefore, drug solubilisation and dissolution are higher when the formulation is mixed with a dairy drink (pH between 6.5 and 6.8; Chapter 3) in comparison with other vehicles due to an increase in the drug ionisation %. For co-administration with soft foods, the highest drug dissolution was observed when the granules were mixed with plain yoghurt (39.3 %) and the lowest when the formulation was mixed with applesauce UK (6.4 %). Drug dissolution differed when vehicles of the same subtype were tested ($AUC_{0\text{-}4h}$ differed between milk/formula, and between squashes, yoghurts and applesauces; $p < 0.05$). The lower drug dissolution observed when the granules were mixed with applesauce UK, in comparison to when mixed with the other soft foods, is probably due to the presence of starch in its composition, which forms a net gel around the formulation that is strengthened by fruit pieces and negatively impacts drug dissolution (13). Results show that vehicles of the same type (*e.g.* soft foods) have a distinct impact on drug dissolution (*e.g.* extremely low to no drug dissolution in the case of mixing with applesauce UK but not when formulation was mixed with plain yoghurt) and it can be hypothesised that this vehicle-impact may, ultimately, affect drug behaviour. This is of particular importance considering that the recommendations for administration of Singulair® granules are to mix with '*a spoonful of cold soft foods'* (27). Therefore, the differences observed in drug dissolution indicate the potential risk of not following vehicle recommendations in clinical practice. Moreover, when evaluating vehicle suitability during drug development, the physicochemical properties of the vehicles should be considered.

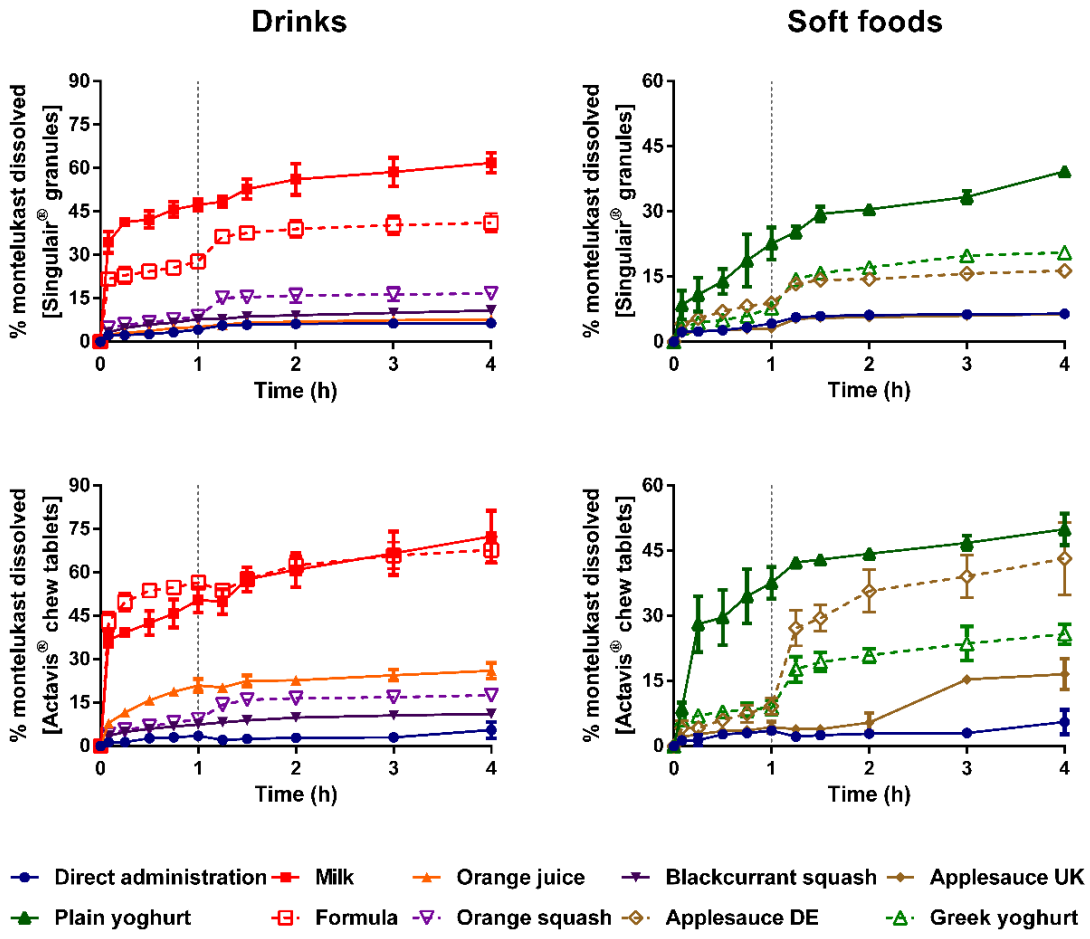


Figure 4.1. Mean % montelukast dissolved (± S.D.) from Singulair® granules (top panel) and Actavis® chewable tablets (bottom panel) after direct administration of formulation, after mixing with selected vehicles (full lines) and with vehicles of the same subtype (dashed lines). Dotted vertical lines represent the time of medium change.

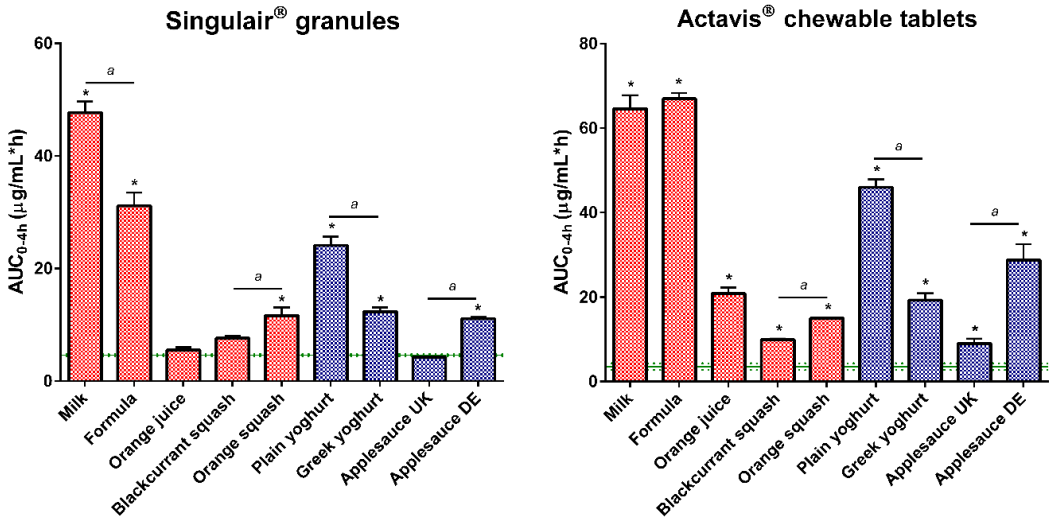


Figure 4.2. Effect of co-administration of formulation with vehicles on % of drug dissolved at 4 h from the tested montelukast formulations. * denotes a statistical difference on drug dissolution between direct administration (dashed line) and co-administration with vehicles

(bars; red: drinks, blue: soft foods). *a* denotes statistical difference when vehicles of the same subtype were tested ($p < 0.05$).

Dissolution of the crushed Actavis® chewable tablets mixed with vehicles resulted in a higher % drug dissolved at 4 h and significantly higher $AUC_{0\text{-}4h}$ in comparison to direct administration of the crushed formulation. Amongst vehicles, drug dissolution was the highest when the crushed tablets were mixed with milk and formula (72.5 and 67.8 %, respectively) and the lowest when the formulation was mixed with blackcurrant squash (11.1 %). Significant differences in $AUC_{0\text{-}4h}$ were revealed between mixing the formulation with milky *vs* fruity drinks, and between mixing with the different squashes tested. Two-fold differences were observed between $AUC_{0\text{-}4h}$ when mixing with vehicles of the same subtype (plain in comparison to Greek yoghurt and between the applesauce UK and applesauce US; $p < 0.05$). These differences could be attributed to the physicochemical properties (*e.g.* different pH and protein content of dairy and fruity drinks, and different viscosity of the applesauces) and macronutrient composition of the vehicles (*e.g.* different sugar content between the squashes), which affect drug solubilisation and may impact drug dissolution behaviour (11).

Dissolution of mesalazine from Pentasa® and Salofalk® granules also revealed a significant effect of co-administration with food and drink vehicles (Figures 4.3 and 4.4). For Pentasa® granules, co-administration with the different vehicles resulted in a lower % drug dissolved at 4 h compared to the direct administration scenario. The calculated $AUC_{0\text{-}4h}$ were significantly lower when the formulation was mixed with vehicles, except blackcurrant squash ($p < 0.05$). For co-administration with drinks, % of drug dissolved (4 h) was higher for mixing with blackcurrant squash and formula (38.1 and 37.9 %, respectively) followed by orange squash (35.5 %), orange juice (24.1 %) and milk (23.4 %). Significant differences in $AUC_{0\text{-}4h}$ were revealed between mixing the Pentasa® granules with milk and formula ($p < 0.05$), but not between mixing with the different squashes tested. For co-administration with soft foods, $AUC_{0\text{-}4h}$ significantly differed when mixing with the different applesauces demonstrating that vehicles of the same subtype can distinctly affect dissolution of different drugs.

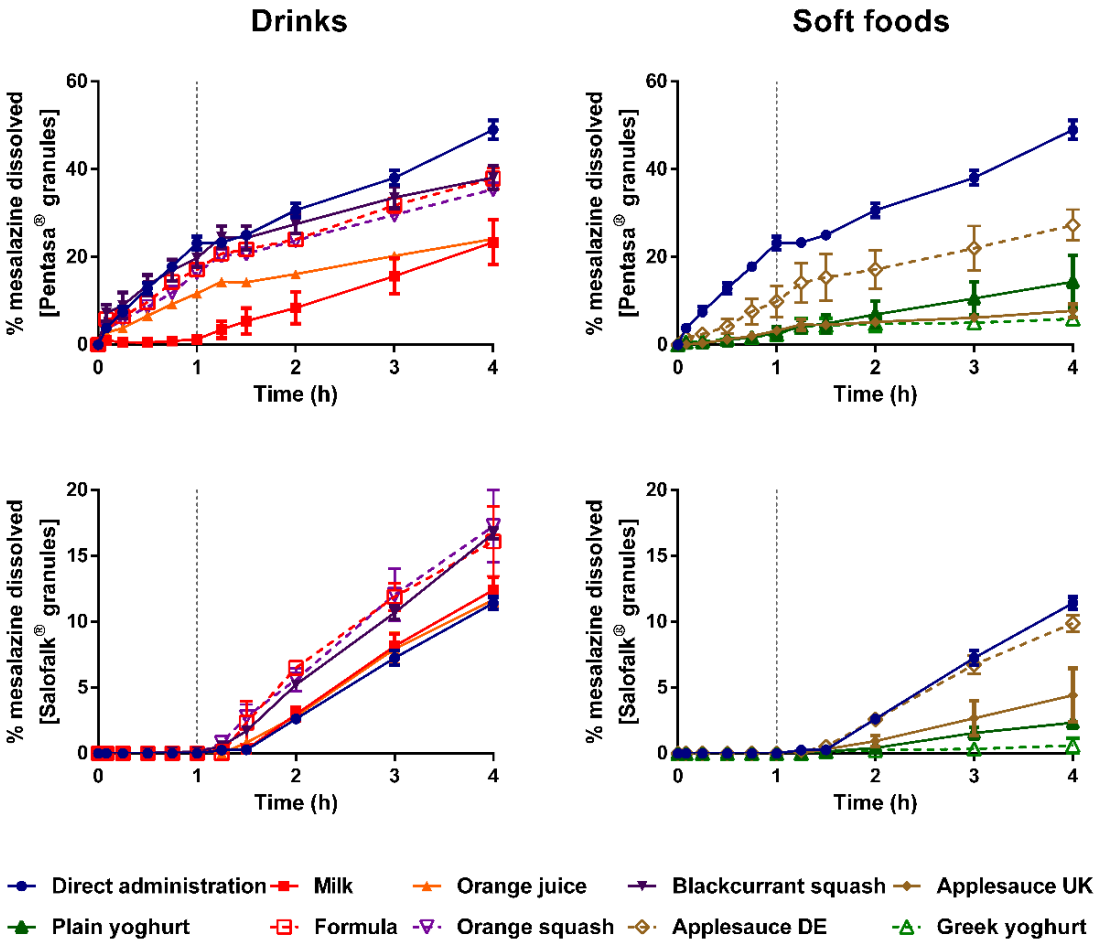


Figure 4.3. Mean % mesalazine dissolved (± S.D.) from Pentasa® (top panel) and Salofalk® granules (bottom panel) after direct administration of formulation, after mixing with selected vehicles (full lines) and with vehicles of the same subtype (dashed lines). Dotted vertical lines represent the time of medium change.

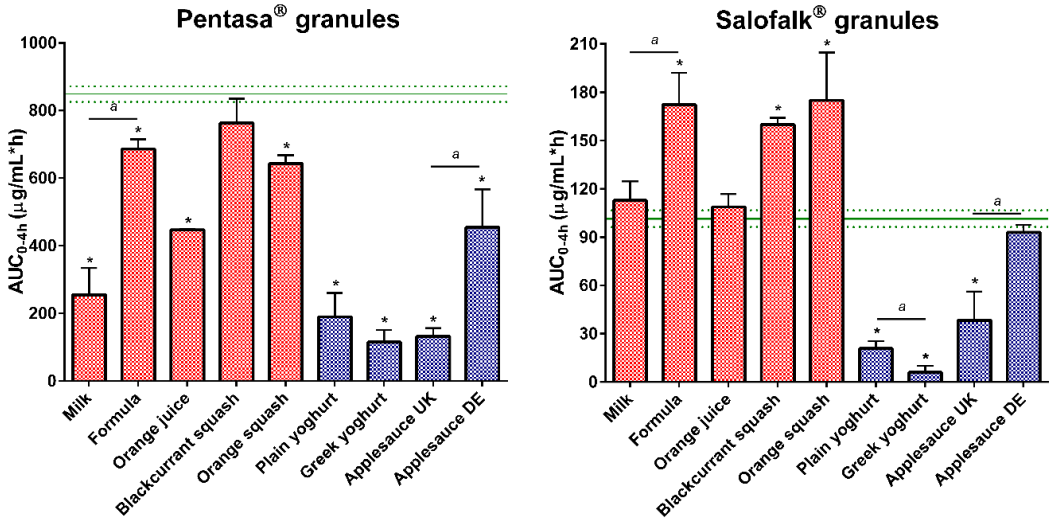


Figure 4.4. Effect of co-administration of formulation with vehicles on % of drug dissolved at 4 h from the tested mesalazine formulations. * denotes a statistical difference on drug

dissolution between direct administration (dashed line) and co-administration with vehicles (bars; red: drinks, blue: soft foods). *a* denotes statistical difference when vehicles of the same subtype were tested ($p < 0.05$).

The % of mesalazine dissolved from Salofalk® granules (4 h) was also affected by the different vehicles used for co-administration. % drug dissolution was the highest when the granules were mixed with orange squash (17.3 %), followed by blackcurrant squash (16.7 %), formula (16.1 %), milk (12.4%), orange juice (11.7 %), direct introduction (11.4 %), and soft foods. $AUC_{0\text{-}4h}$ was significantly different for the direct administration scenario compared to co-administration with vehicles, except milk, orange juice and applesauce DE ($p > 0.05$). For co-administration with soft foods, % of drug dissolved at 4 h was the lowest when the formulation was mixed with Greek yoghurt (0.6 %) and the highest when mixed with applesauce DE (9.9 %), indicating that vehicles of the same type (*e.g.* soft foods) have a distinct impact on drug dissolution. The lower drug dissolution observed when the granules were mixed with soft foods was likely due to a physical barrier that these vehicles create around the formulation, which prevents mixing with GI fluids and hinders drug release, ultimately, reducing drug exposure at the site of absorption (13). Dissolution of mesalazine from Salofalk® granules also differed when mixed with vehicles of the same subtype; namely, applesauce UK *vs* US, milk *vs* formula, and plain *vs* Greek yoghurt ($p < 0.05$).

Interestingly, the two mesalazine formulations were oppositely affected when mixed with drinks compared to direct introduction of the granules: for Pentasa® drug dissolution was lower, whereas for Salofalk® granules was higher. The mode of drug release of the two formulations is different; Pentasa® granules have a pH-independent extended release, whereas Salofalk® granules have a pH-dependent delayed release (Table 4.1). Therefore, the vehicle-impact on drug dissolution from different formulations will depend not only on vehicle properties, but also on formulation properties (*e.g.* differences in the mode of drug release, type of dosage form).

Overall, it was possible to observe a significant effect of medicine co-administration with soft foods and drinks on the dissolution of both drugs from all the formulations tested. Results show a vehicle-induced impact on drug dissolution due to changes in

drug ionisation % and, consequently, drug solubility (*e.g.* higher % montelukast dissolved when formulation is mixed with milk), changes in formulation environment (*e.g.* higher viscosity of applesauce hindering drug release/dissolution), and alteration of formulation factors (*e.g.* different coating of the tested mesalazine granules).

3.2 Assessment of the impact of different administration practices on drug dissolution behaviour

Delaying testing by 4 h after mixture preparation revealed significant differences on drug dissolution in comparison to testing immediately after mixing (montelukast: Figures 4.5 and 4.6; mesalazine: Figures 4.7 and 4.8). For Singulair® granules, delaying testing by 4 h after mixing led to a higher % drug dissolved and a significantly higher $AUC_{0\text{-}4h}$ for co-administration with milk, orange juice and applesauce UK ($p < 0.05$). This is probably due to the solubility of montelukast in these vehicles, which resulted in an increased drug solubilisation and dissolution during the 4 h delay (11). From the 3 cases, the differences in drug dissolution between the two testing scenarios were most accentuated when the granules were mixed with milk. As observed in section 3.1, this is probably due to the pH of milk which leads to an increase in drug solubilisation and dissolution, in comparison to when the granules are mixed with other vehicles. Results from this test show that this increase is even more evident if there is a delay between preparation and administration of the mixture. In contrast, delaying testing after mixing the Singulair® granules with blackcurrant squash had no effect on drug dissolution, whereas delaying the time between mixing with plain yoghurt and testing resulted in a significantly lower $AUC_{0\text{-}4h}$. Delaying testing by 4 h after mixing the granules with applesauce UK and plain yoghurt led to a drop in drug concentration after the media change from SGF*sp* pH1.2 to SIF*sp* pH 6.8. This might be related to the sudden change in pH and increase in media volume (10).

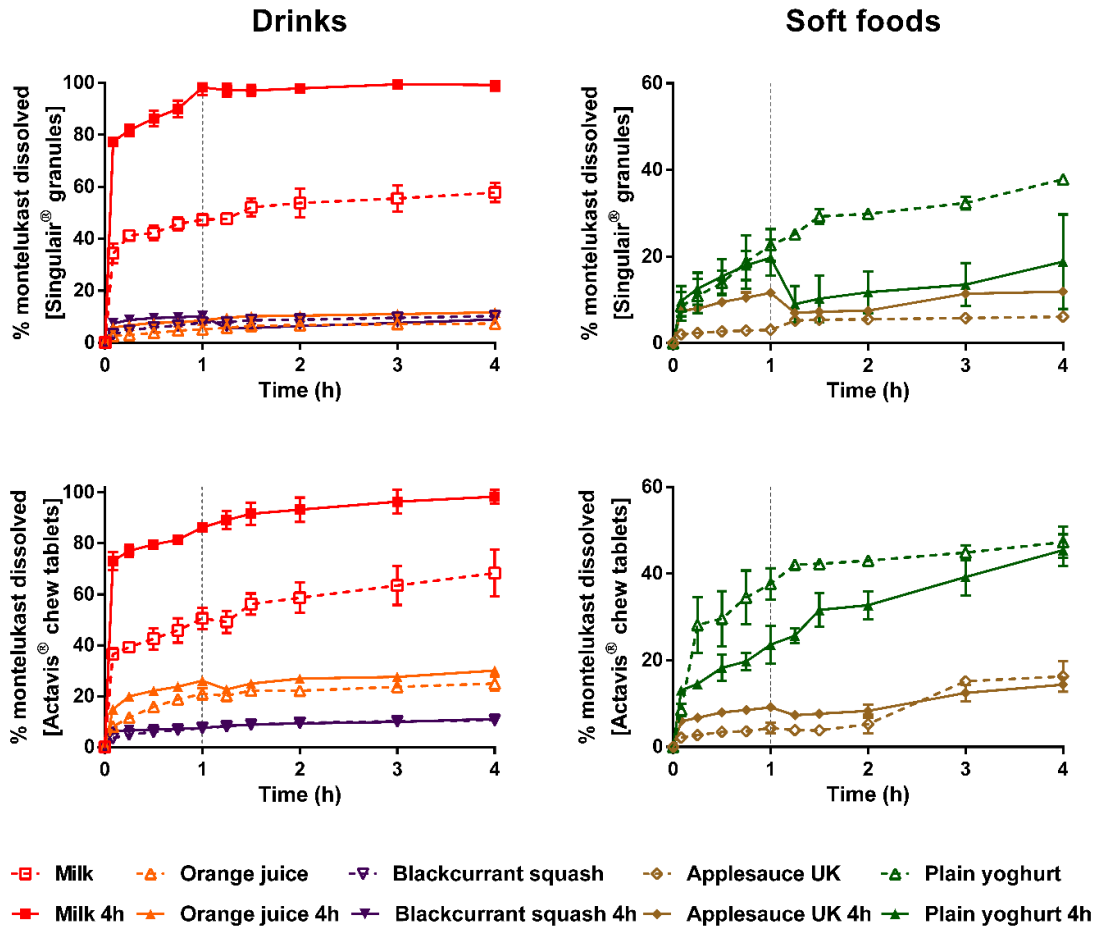


Figure 4.5. Mean % montelukast dissolved (± S.D.) from Singulair® granules (top panel) and Actavis® chewable tablets (bottom panel), under two administration scenarios: testing immediately after mixing (dashed lines) and 4 h after mixing (full lines). Dotted vertical lines represent the time of medium change.

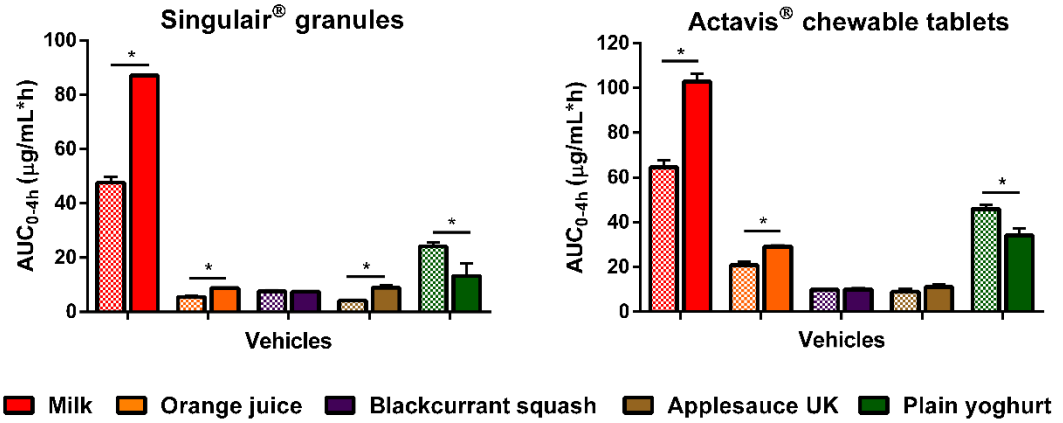


Figure 4.6. Effect of a 4 h delay between mixing and testing of formulation with vehicles on drug dissolution from the tested montelukast formulations. * denotes a statistical difference on drug dissolution between testing immediately after mixing (dashed bars) and testing 4 h after mixing (full bars).

For the crushed Actavis® chewable tablets, a 4 h delay between mixing the formulation with the vehicles and testing resulted in a higher % drug dissolved for co-administration with vehicles, apart from when the formulation was mixed with blackcurrant squash, applesauce and plain yoghurt. $AUC_{0\text{-}4h}$ was significantly different when the crushed chewable tablets were mixed with milk, orange juice (both higher) and plain yoghurt (lower), in comparison to immediate administration of the vehicle-formulation mixtures ($p < 0.05$).

For Pentasa® granules, increasing the time between preparation and testing of the granules-vehicle mixtures resulted in a higher % drug dissolved (4 h), and significantly higher $AUC_{0\text{-}4h}$, when the formulation was mixed with milk, applesauce UK and plain yoghurt.

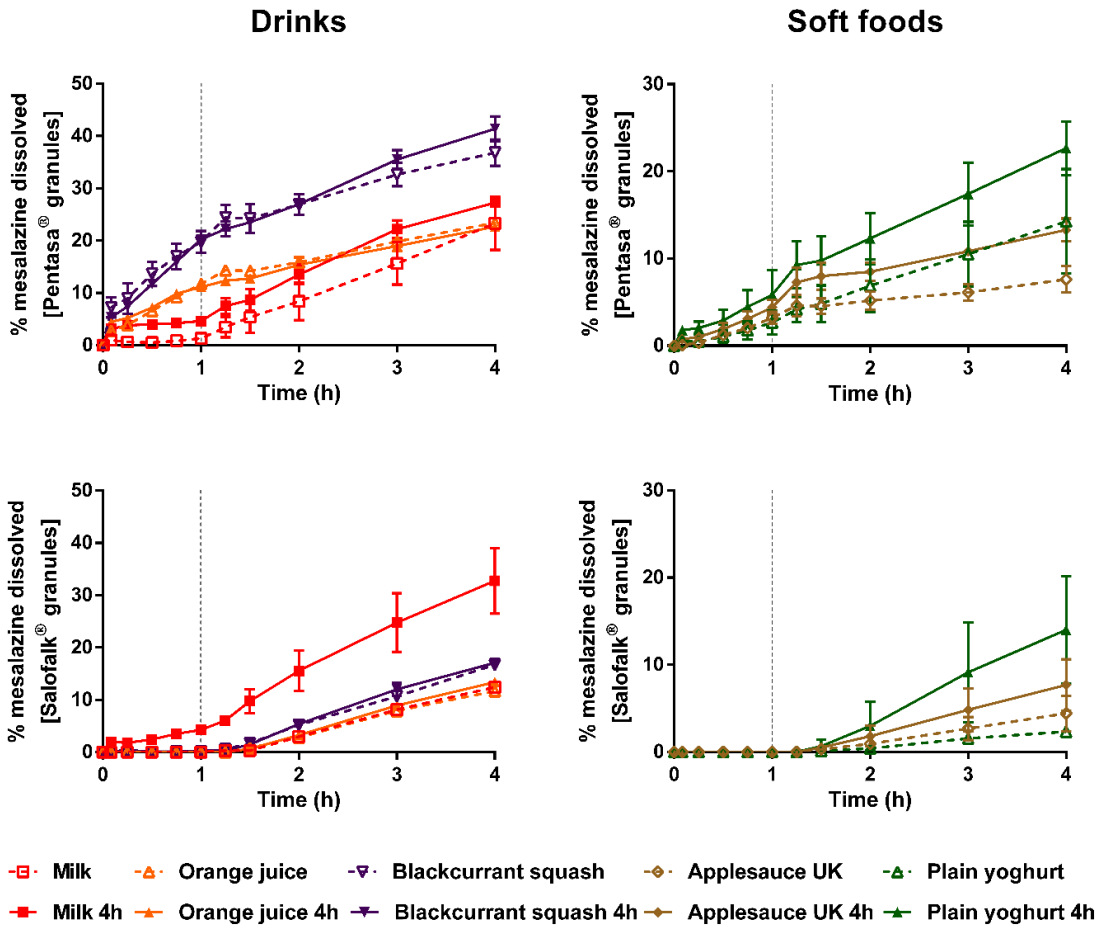


Figure 4.7. Mean % mesalazine dissolved (± S.D.) from Pentasa® granules (top panel) and Salofalk® granules (bottom panel) under two administration scenarios: testing immediately after mixing (dashed lines) and 4 h after mixing (full lines). Dotted vertical lines represent the time of medium change.

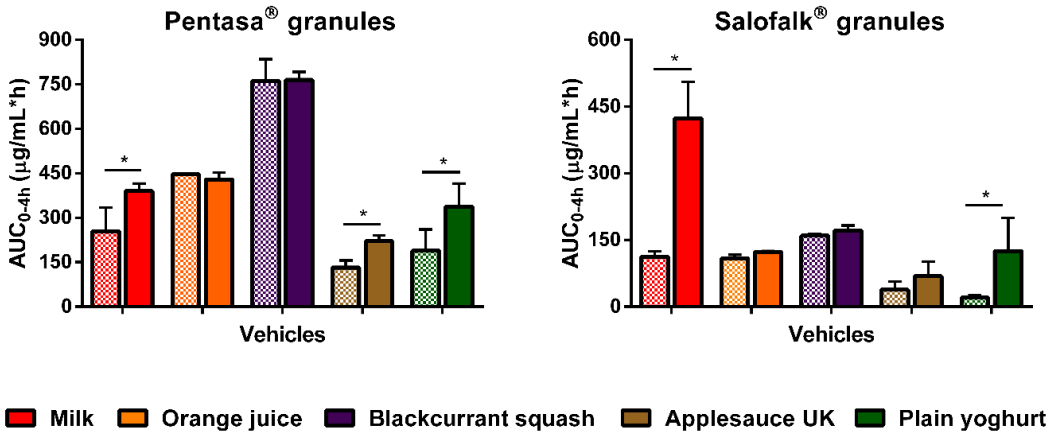


Figure 4.8. Effect of a 4 h delay between mixing and testing of formulation with vehicles on drug dissolution from the tested mesalazine formulations. * denotes a statistical difference on drug dissolution between testing immediately after mixing (dashed bars) and testing 4 h after mixing (full bars).

For Salofalk® granules, increasing the time between mixing the formulation with milk and testing resulted in a significantly higher $AUC_{0\text{-}4h}$ and 3-fold increase on % drug dissolved (4 h), observed from the beginning of dissolution (pH 1.2). The Salofalk® granules have a pH-dependent modified release coating (due to the presence of the coating polymers Eudragit L and NE 40 D which only disintegrate at pH ≥ 6), and therefore no release is intended during the gastric passage. A 4 h delay between mixing the granules with milk (pH 6.8) and testing resulted in a pH-induced loss of integrity of the coating and, consequently, earlier drug release and dissolution. In contrast, the 4 h delay between mixing the Salofalk® granules with the other vehicles (pH between 2 and 4.5; Chapter 3) and testing did not alter drug dissolution in the first hour of the test (pH 1.2) due to the polymer coating. $AUC_{0\text{-}4h}$ was significantly higher when delaying testing after mixing the formulation with plain yoghurt (pH 4.5) ($p < 0.05$). This testing scenario was also associated with large variation in dissolution between replicate tests, probably due to the loss of integrity of the formulation during the mixing which resulted in an unimpaired release.

Overall, results indicate that when medicines are co-administered with vehicles, the mixtures should be administered as soon as possible after preparation, unless specific data is available and indicated, not only due to risk of dosing errors and potential microbiological contamination, but also due to other vehicle-effects on drug dissolution (*e.g.* increased drug solubilisation, potential stability issues). Depending

on the formulation, and particularly for enteric-coated dosage forms (case study, Salofalk®), delaying administration of the prepared formulation-vehicle mixture could result in changes in drug absorption and, consequently, drug safety and efficacy. Other potential consequences of delaying the administration of the drug-vehicle mixture are an increase of the risk of adverse side effects, depending on the drug category (*e.g.* for nonsteroidal anti-inflammatory drugs, it might lead to irritation of the GI mucosa and, ultimately, ulcers) (13).

3.3 Assessing the impact of *in vitro* hydrodynamics

In vitro drug dissolution from the formulations tested (montelukast: Singulair® granules; mesalazine: Pentasa® granules) was influenced by the hydrodynamic conditions, for all the scenarios tested (Figures 4.9 and 4.10). For Singulair® granules, higher agitation conditions resulted in a higher % drug dissolved (4 h) when the formulation was mixed with milk, orange juice, applesauce and plain yoghurt (drug dissolved = 78.0 %, 35.3 %, 7.8 % and 47.9 %, respectively). Analysis of the $AUC_{0\text{-}4h}$ revealed significant differences when comparing low (50 rpm) and high (100 rpm) testing agitation rates in all cases, apart from the direct introduction scenario. A significantly higher $AUC_{0\text{-}4h}$ was observed when the granules were mixed with milk, orange juice, applesauce UK and plain yoghurt and tested at 100 rpm, in comparison to 50 rpm (Figure 4.10). This is probably related to the effect of the increased hydrodynamics, which result in a better dispersion of the drug product-vehicle mixture and, consequently, facilitate drug dissolution from the vehicles (36). For the scenarios of direct administration and mixing with blackcurrant squash, drug dissolution was likely limited by the drug solubility in the media and not as affected by the increase in agitation rate (11).

Testing at 100 rpm also resulted in a higher drug dissolution and significantly higher $AUC_{0\text{-}4h,}$ when the Pentasa® granules were mixed with milk, orange juice, plain yoghurt and applesauce, compared to 50 rpm ($p < 0.05$).

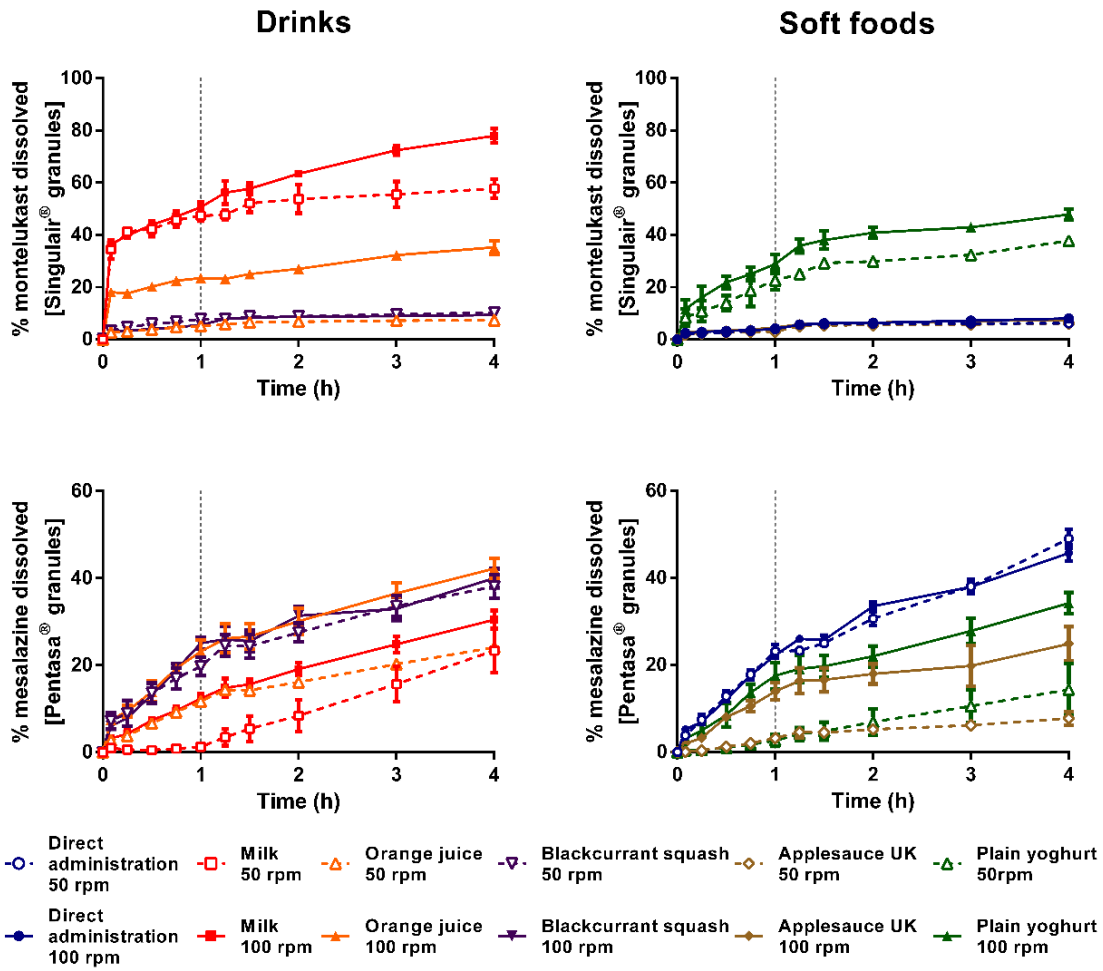


Figure 4.9. Mean % drug dissolved (± S.D.) of montelukast from Singulair® granules (top panel) and mesalazine from Pentasa® granules (bottom panel), after testing under two agitation rate conditions: 50 rpm (dashed bars) and 100 rpm (full bars). Dotted vertical lines represent the time of medium change.

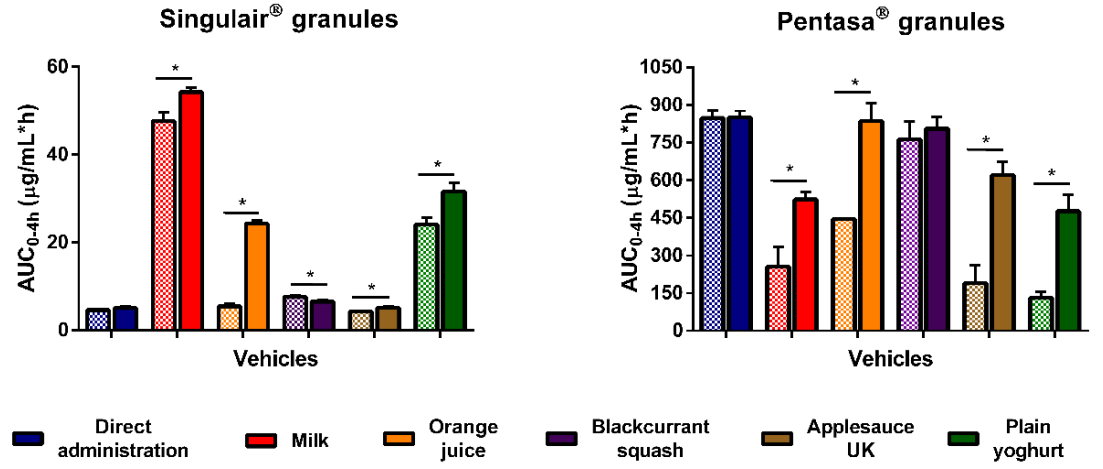


Figure 4.10. Effect of dissolution hydrodynamics on $AUC_{0\text{-}4h}$ of Singulair® (montelukast) and Pentasa® (mesalazine) granules. * denotes a statistical difference in $AUC_{0\text{-}4h}$ between drug dissolution when agitation rate was set at 50 (dashed bars) and 100 rpm (full bars).

In comparison to the results obtained when testing at 50 rpm, increasing the agitation rate to 100 rpm resulted in a reduced discrimination between drug dissolution profiles. Nevertheless, comparison of $AUC_{0\text{-}4h}$ of the dissolution profiles obtained at 100 rpm still revealed significant differences between direct introduction of the formulation and mixing with vehicles ($p < 0.05$). Therefore, the differences in drug dissolution for co-administration with vehicles in comparison to direct administration of formulation were not due to the agitation speed set (50 rpm) since they were still observed when testing at a higher agitation rate.

3.4 Statistical evaluation of the factors impacting *in vitro* drug dissolution

Results from the PLS-R analyses, conducted to understand the vehicle impact on the dissolution of the two drugs, are shown in Figure 4.11. For the dissolution of montelukast from the granules and crushed chewable tablets, the PLS-R model developed was defined by 3 components and showed a good fit to the experimental values ($R^2 = 0.83$) and a good predictive power ($Q^2 = 0.79$). The statistical analysis revealed that vehicle pH and percentage of fat and drug solubility in each vehicle were the factors with the most significant positive impact on drug dissolution from the two montelukast formulations tested, with a moderate negative impact from vehicle osmolality, viscosity, percentage of sugar and of protein.

For dissolution of mesalazine, the model constructed was defined by 2 components and showed a good fit to the experimental values ($R^2 = 0.70$) and a good prediction power ($Q^2 = 0.64$). PLS-R analysis revealed that the type of formulation was the factor with the most significant positive impact on drug dissolution, while significant negative effects from vehicle viscosity, percentage of protein and buffer capacity were observed. Moderate negative effects from vehicle osmolality, percentage of sugars and drug solubility were also observed.

For dissolution of both drugs (all formulations), the PLS-R model built was defined by 6 compartments, had good predictive power and showed a good fit to the experimental values ($Q^2 = 0.62$ and $R^2 = 0.70$, respectively). PLS-R analysis showed that the drug characteristics (logP and ionisation %), and the pH of the vehicles were the factors with a significant negative effect on drug dissolution. A moderate negative effect from vehicle buffer capacity was also observed. In contrast,

significant positive effects from the type of formulation, drug solubility in each vehicle and percentage of fat of the vehicle were observed. Moderate positive effects from vehicle osmolality, viscosity and percentage of protein were also observed.

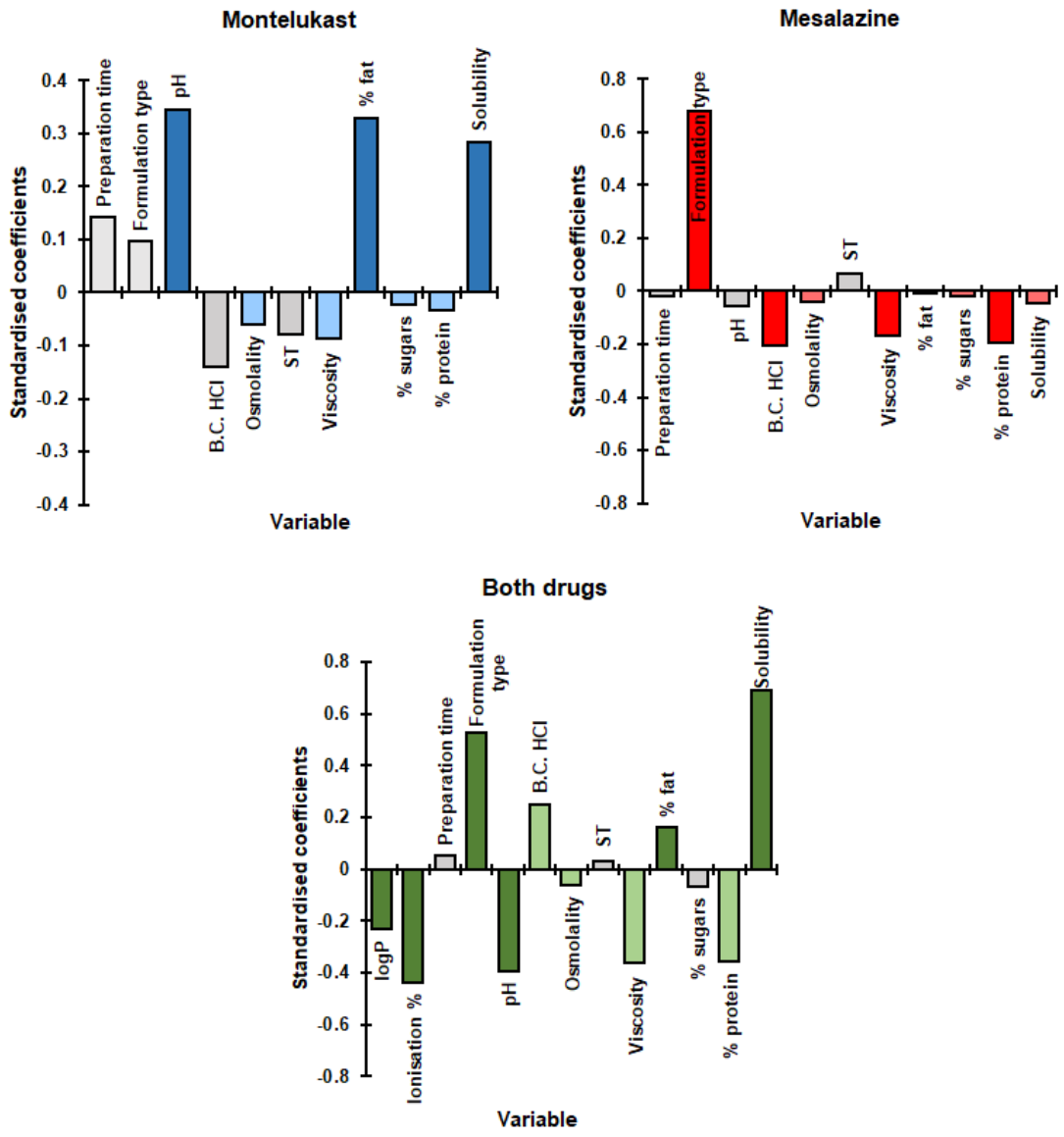


Figure 4.11. Standardised coefficients corresponding to the variables studied for dissolution of montelukast, mesalazine and both drugs. Colour denotes coefficients with a moderate (lighter colour) and significant (darker colour) impact on the response (VIP > 0.7 and 1, respectively). [B.C. = buffer capacity; ST = surface tension]

Overall, PLS-R results showed that knowledge of the physicochemical properties and macronutrient composition of the food and drinks and drug/formulation properties can help understand the potential vehicle-impact on drug dissolution. This

impact should be taken into consideration during compatibility assessments of the vehicle-drug product and could be used to predict potential alterations on drug product behaviour.

4. Conclusions

For poorly soluble drugs, *in vivo* dissolution is likely to be the rate-limiting step of *in vivo* drug absorption and bioavailability. This study aimed to assess the impact of practices of medicine co-administration with food and drinks on the dissolution behaviour of two compounds. Results show that vehicle-induced changes on drug ionisation % and solubility (affected by the pH of the different vehicles), formulation environment (*e.g.* higher viscosity of the soft foods), and alteration of formulation factors (*e.g.* different coating of the mesalazine granules) affect drug dissolution behaviour. Drug dissolution was significantly affected by both the different vehicles as well as the timing between preparation and testing of the vehicle-drug product mixtures. The use of different vehicles may impact the pharmacokinetic profile of the drug, ultimately altering its clinical performance. For example, alterations in drug bioavailability related to reduced dissolution rates are of concern for drugs that display dissolution as a rate limiting step of absorption, and have a narrow therapeutic index (as the absorbed concentration needed to induce a therapeutic effect may not be reached) or when immediate release is required for fast therapeutic action. Increased drug bioavailability may lead to drug toxicity and adverse clinical side effects. Therefore, it is essential to consider the nature of the vehicles commonly used in practice and the possible effects of different administration recommendations on product performance and, ultimately, clinical performance.

The age-appropriate *in vitro* dissolution test used in this study is a useful biopharmaceutical tool for estimating drug dissolution in conditions relevant to infants. Due to the simplistic experimental setup, it is possible to address paediatric administration scenarios (as done in the current study), as well as testing parameters representative of the different paediatric subgroups (*e.g.* by using different volumes, agitation rate and media change times). Although it cannot entirely replace *in vivo* testing, the dissolution setup described has the potential to provide information on

the impact of medicine co-administration with vehicles on paediatric formulation performance and is a useful tool for identifying risks associated with this practice.

References

1. Richey RH, Shah UU, Peak M, Craig JV, Ford JL, Barker CE, et al. Manipulation of drugs to achieve the required dose is intrinsic to paediatric practice but is not supported by guidelines or evidence. BMC Pediatr. 2013;13(1):81.

2. Turner MA, Catapano M, Hirschfeld S, Giaquinto C. Paediatric drug development: the impact of evolving regulations. Adv Drug Deliv Rev. 2014;73:2-13.

3. Martir J, Flanagan T, Mann J, Fotaki N. Recommended strategies for the oral administration of paediatric medicines with food and drinks in the context of their biopharmaceutical properties: a review. J Pharm Pharmacol. 2017;69(4):384-97.

4. Akram G, Mullen AB. Paediatric nurses' knowledge and practice of mixing medication into foodstuff. Int J Pharm Pract. 2012;20(3):191-8.

5. Venables R, Stirling H, Batchelor H, Marriott J. Problems with oral formulations prescribed to children: a focus group study of healthcare professionals. Int J Clin Pharm. 2015;37(6):1057-67.

6. Ernest TB, Craig J, Nunn A, Salunke S, Tuleu C, Breitkreutz J, et al. Preparation of medicines for children - a hierarchy of classification. Int J Pharm. 2012;435(2):124-30.

7. Lippert C, Gbenado S, Qiu C, Lavin B, Kovacs SJ. The bioequivalence of telithromycin administered orally as crushed tablets versus tablets swallowed whole. J Clin Pharmacol. 2005;45(9):1025-31.

8. Paradiso LM, Roughead E, Gilbert A, Cosh D, Nation R, Barnes L, et al. Crushing or altering medications: what's happening in residential aged-care facilities? Australas J Ageing. 2002;21(3):123-7.

9. Wells KA, Losin WG. In vitro stability, potency, and dissolution of duloxetine enteric-coated pellets after exposure to applesauce, apple juice, and chocolate pudding. Clin Ther. 2008;30(7):1300-8.

10. Martir J, Flanagan T, Mann J, Fotaki N. Stability of paediatric drugs co-administered with different foods and drinks. 2017. Abstract from AAPS annual meeting, San Diego, USA.

11. Martir J, Flanagan T, Mann J, Fotaki N. Impact of co-administration of food and drink vehicles on the solubility of poorly soluble paediatric drugs. 2017. Abstract from AAPS annual meeting, San Diego, USA.

12. Van Zwieten P. Amlodipine: an overview of its pharmacodynamic and pharmacokinetic properties. Clin Cardiol. 1994;17(9 Suppl 3):III3.

13. Manrique YJ, Lee DJ, Islam F, Nissen LM, Cichero JA, Stokes JR, et al. Crushed tablets: does the administration of food vehicles and thickened fluids to aid medication swallowing alter drug release? J Pharm Pharm Sci. 2014;17(2):207-19.

14. Endrenyi L, Tothfalusi L. Determination of bioequivalence for drugs with narrow therapeutic index: reduction of the regulatory burden. J Pharm Pharm Sci. 2013;16(5):676-82.

15. Wishart DS, Knox C, Guo AC, Cheng D, Shrivastava S, Tzur D, et al. DrugBank: a knowledgebase for drugs, drug actions and drug targets. Nucleic Acids Res. 2007;36(suppl_1):D901-D6.

16. Drug Delivery Foundation. BCS database. 2015. http://www.tsrlinc.net/search.cfm. Assessed 5 November 2018.

17. Benet LZ, Broccatelli F, Oprea TI. BDDCS applied to over 900 drugs. AAPS J. 2011;13(4):519-47.

18. Carrier M-N, Garinot O, Vitzling C. Stability and compatibility of tegaserod from crushed tablets mixed in beverages and foods. Am J Health Syst. 2004;61(11):1135-42.

19. Belard S, Isaacs W, Black F, Bateman L, Madolo L, Munro J, et al. Treatment of childhood tuberculosis: caregivers' practices and perceptions in Cape Town, South Africa. Paediatr Int Child Health 2015;35(1):24-8.

20. Best BM, Capparelli EV, Diep H, Rossi SS, Farrell MJ, Williams E, et al. Pharmacokinetics of lopinavir/ritonavir crushed versus whole tablets in children. J Acquir Immune Defic Syndr. 2011;58(4):385-91.

21. Food and Drug Administration. Center for Drug Evaluation and Research, Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments - Draft Guidance for Industry. 2018. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM614401.pdf. Accessed 6 October 2018.

22. Fotaki N, Vertzoni M. Biorelevant dissolution methods and their applications in in vitro-in vivo correlations for oral formulations. Open Drug Deliv J. 2010;4(2):2-13.

23. Shah VP. Progressive applications of dissolution, its impact, and implications in the pharmaceutical world. J Pharm Sci. 2013;102(9):2895-7.

24. Kostewicz ES, Abrahamsson B, Brewster M, Brouwers J, Butler J, Carlert S, et al. In vitro models for the prediction of in vivo performance of oral dosage forms. Eur J Pharm Sci. 2014;57:342-66.

25. Guimarães M, Statelova M, Holm R, Reppas C, Symilllides M, Vertzoni M, et al. Biopharmaceutical considerations in paediatrics with a view to the evaluation of orally administered drug products–a PEARRL review. J Pharm Pharmacol. 2019;71(4):603-42.

26. Martir J, Flanagan T, Mann J, Fotaki N. Characterisation of the physicochemical properties of food and drinks used for the co-administration of

drugs in the paediatric population. 2017. Abstract from AAPS annual meeting, San Diego, USA.

27. BNF for Children (BNFC) 2016-2017: Royal Pharmaceutical Society of Great Britain, British Medical Association, Pharmaceutical Press; 2017.

28. USP 30- NF 25. United States Pharmacopeia Convention. Rockville, USA; 2007.

29. Fiolka T, Dressman J. Development, current applications and future roles of biorelevant two-stage in vitro testing in drug development. J Pharm Pharmacol. 2018;70(3):335-48.

30. Jensen J, Cornett C, Olsen CE, Tjørnelund J, Hansen SH. Identification of major degradation products of 5-aminosalicylic acid formed in aqueous solutions and in pharmaceuticals. Int J Pharm. 1992;88(1-3):177-87.

31. Smith GA, Rawls CM, Kunka RL. An automated method for the determination of montelukast in human plasma using dual-column HPLC analysis and peak height summation of the parent compound and its photodegradation product. Pharm Res. 2004;21(9):1539-44.

32. Raju KN, Swamy TG, Rao AL. Development and validation of RP-HPLC method for the determination of montelukast sodium in bulk and in pharmaceutical formulation. J Pharm Chem Biol Sci. 2011;1(1):12-6.

33. Fadda H, Sousa T, Carlsson A, Abrahamsson B, Williams J, Kumar D, et al. Drug solubility in luminal fluids from different regions of the small and large intestine of humans. Mol Pharm. 2010;7(5):1527-32.

34. Wold S, Sjöström M, Eriksson L. PLS-regression: a basic tool of chemometrics. Chemometr Intell Lab Syst. 2001;58(2):109-30.

35. Thibert R, Mach H, Clas S-D, Meisner DR, Vadas EB. Characterization of the self-association properties of a leukotriene D4 receptor antagonist, MK-0476. Int J Pharm. 1996;134(1-2):59-70.

36. Klein S, Shah VP. A standardized mini paddle apparatus as an alternative to the standard paddle. AAPS PharmSciTech. 2008;9(4):1179-84.

Chapter 5: Predictive biorelevant dissolution testing of montelukast formulations administered with drinks and soft foods to infants

Abstract

Objectives: The aim of this study was to develop a predictive biorelevant dissolution test in order to investigate the impact of medicine co-administration with soft food and drinks on the dissolution performance of a poorly soluble compound. Relevant *in vitro* dissolution conditions simulating the *in vivo* gastrointestinal environment of infants were used to establish *in vitro-in vivo* relationships with corresponding *in vivo* data.

Methods: Dissolution studies of two montelukast formulations were conducted with the mini-paddle apparatus on a two-stage approach: infant fasted state simulated gastric fluid (Pi-FaSSGF; for 1 h) followed by either fasted state or infant fed state simulated intestinal fluid (FaSSIF-V2 or Pi-FeSSIF, respectively; for 3 h). The dosing scenarios tested reflected *in vivo* paediatric administration practices: (i.) direct administration of formulation; (ii.) formulation co-administered with vehicles (formula, milk or applesauce).

Key findings: In comparison with direct administration of formulation, drug dissolution was significantly affected by co-administration with vehicles. Drug dissolution was significantly higher when testing under fed state intestinal conditions in comparison to the fasted state. A good relationship was revealed between the i*n vitro* drug dissolution (Pi-FaSSGF/Pi-FeSSIF conditions) and the *in vivo* drug performance in all subgroups when testing the granules with milk, and in the 1 to 3 months subgroup with the granules-formula mixture. Moreover, although the *in vivo* prandial state of the infants was not evident, findings indicate that the studies were either performed in the fed state or the practice of co-administration with vehicles might trigger fed state conditions *in vivo*.

Conclusions: Ultimately, this study supports the potential utility of the biorelevant *in vitro* dissolution approach proposed to predict the *in vivo* formulation performance after co-administration with vehicles, in the paediatric population.

1. Introduction

Understanding the dissolution profile of a pharmaceutical dosage form and linking it to its *in vivo* pharmacokinetic (PK) profile is a vital requirement for ensuring product quality and safety of use (1-3). Dissolution profiles can be analysed through different approaches: using model-dependent methods where experimental data are fitted using mathematical equations, model-independent methods (single values such as mean dissolution time and area under the dissolution curve (AUC) are used for data evaluation), and/or statistical methods (*e.g.* ANOVA and multivariate analysis) (4, 5).

Drug dissolution profiles may be used to establish *in vitro-in vivo* correlations (IVIVC). The development of an IVIVC for a pharmaceutical dosage form is of great interest to the pharmaceutical industry and plays a key role in the pharmaceutical development of dosage forms (1). It can serve as a surrogate for *in vivo* bioavailability and be used to request biowaiver status for formulations or production changes within a product lifecycle (1-3). This reduces the need for expensive bioequivalence (BE) testing in humans.

Defining appropriate biorelevant drug dissolution conditions requires an understanding of the relationship between the various physicochemical and physiological factors that have an impact on the rate and extent to which an orally administered dosage form is absorbed (4). Since clinical research with adults cannot simply be generalised or extrapolated to the paediatric population, research involving paediatric patients is essential (6). Age-related PK studies are normally required due to differences in anatomy or drug handling/manipulation practices, which might lead to different dose requirements to achieve efficacy or to avoid adverse effects (7). Moreover, changes in developmental physiology throughout childhood complicate pharmacotherapy, due its impact on drug absorption, distribution, metabolism and excretion of drugs and excipients (8). Thus, better understanding of physiological developmental changes is important for paediatric drug testing. Challenges in paediatric medicine development include: (i.) the need for appropriate outcome measures for paediatric patients, (ii.) the complexities of paediatric administration practices (*e.g.* drug manipulation and mixing with food and drinks (vehicles)), (iii.)

the parental involvement, and (iv.) the adaptations of required research procedures and settings to accommodate paediatric anatomic/cognitive development (8).

Development of a physiologically relevant *in vitro* dissolution setup would be crucial for the prediction of the *in vivo* performance after the administration of a formulation to a paediatric patient. Moreover, it would be beneficial for the investigation of formulation sensitivity to different foods and drinks, so that the risks associated with its co-administration can be predicted. In 2018, the FDA issued a draft guidance addressing the recommended approaches for determination of the suitability of the vehicles intended for co-administration of paediatric medicines. In this guidance, standardised *in vitro* methods for evaluating possible vehicle-effects on *in vivo* product performance were described (9). These tests could help reduce the number of *in vivo* studies required for paediatric formulation development, and ultimately help tackle ethical issues related to paediatric clinical research (10). To this extent, *in vitro* test conditions should address the parameters relevant to drug release and dissolution in the paediatric gastrointestinal (GI) tract, including media composition, prandial state, hydrodynamics and current administration practices. The possible effect of these parameters on the *in vivo* drug behaviour should be considered during paediatric drug development (6, 11). Recently, *in vitro* dissolution studies, performed with a mini-paddle apparatus and a two-stage approach, showed that this setup could be a useful biopharmaceutical tool for estimating drug release/dissolution in paediatric conditions (Chapter 4). With this setup it is possible to address pH, fluid composition and volumes and transit times representative of the GI tract of infants, as well as different paediatric administration practices such as medicine co-administration with food and drinks.

The aims of this study were (i.) to investigate the impact of co-administration of montelukast formulations (granules and chewable tablets) with food and drinks on drug dissolution performance, under paediatric physiological relevant conditions, and (ii.) to evaluate the *in vitro* dissolution studies in terms of their predictability of the *in vivo* formulation performance.

Montelukast was chosen as the model drug; it is an amphoteric compound, with a high lipophilicity (clogP 8.79), and classified as BCS class II (12). Montelukast is a potent leukotriene receptor antagonist that has demonstrated efficacy and tolerability

in the treatment of patients with chronic asthma (13-15). For approved paediatric use, it is available in two dosage forms (granules and chewable tablets) and is used in very young ages from 1 month old (15). The PK profile of montelukast is dose proportional and not substantially altered by age (16). As shown in different *in vivo* studies in infant subgroups, montelukast formulations are often mixed with drinks or soft foods to facilitate administration (7, 14, 15, 17).

2. Materials and methods

2.1 Materials

Ammonium acetate [High Performance Liquid Chromatography (HPLC) grade], 37% hydrochloric acid, sodium hydroxide, sodium chloride, glacial acetic acid and maleic acid were purchased from Fisher Scientific (UK). Dichloromethane, acetonitrile (HPLC grade) and methanol (HPLC grade) were from VWR Chemicals (UK). Montelukast sodium (pharmaceutical secondary standard), sodium oleate and pepsin from porcine gastric mucosa (Ph. Eur.) were obtained from Sigma-Aldrich Company Ltd (UK). Sodium taurocholate (Prodotti Chimici Alimentari S.P.A., Italy), egg lecithin Lipoid EPCS (Lipoid E PCS, Phosphatidylcholine from egg; from Lipoid GmbH, Germany) and glyceryl monooleate – Rylo Mg 19 (Danisco, Denmark) were used. Water was ultra-pure (Milli-Q) laboratory grade. Regenerated cellulose [RC] membrane filters (0.45 µm) (Cronus®, UK), filter papers (0.45 µm) and glass microfiber [GF/D] filters (2.7 µm) (Whatman®, UK), and porous full flow polyethylene cannula filters (10 µm) (Quality Lab Accessories LCC, USA) were used. Full fat U.H.T. milk was purchased from The Co-Operative (UK), First Infant Milk (cow's milk-based formula) was from Cow & Gate (UK) and Bramley applesauce Colman's of Norwich from Unilever (UK). Singulair® Pediatric granules (4 mg, 28 sachets; from Merck Sharp & Dohme Ltd, UK), and Actavis® chewable tablets (5 mg, 28 chewable tablets; from Actavis, UK) were kindly donated by AstraZeneca (UK).

2.2 Methods

2.2.1 Dissolution media preparation

Paediatric biorelevant media representative of infants were freshly prepared for each experiment, as described by Maharaj *et al* (18). Infant Fasted-State Simulated Gastric Fluid (Pi-FaSSGF, pH 1.6), and Fasted-State Simulated Intestinal Fluid (FaSSIF-V2, pH 6.5) or infant Fed-State Simulated Intestinal Fluid (Pi-FeSSIF, pH 5.8) were used. Both fasted and fed intestinal state were simulated since the prandial state of the infant patients in the *in vivo* studies was not reported, and in order to investigate if medicine co-administration with a vehicle would induce a food effect in the infant. Double concentrated simulated intestinal fluids were prepared for the two-stage dissolution studies performed (section 2.2.3).

2.2.2 Sample preparation

Formula was prepared as per manufacturer's instructions: 1 scoop of powder (approximately 4.5 g) was added to 30 mL of boiled cooled water. Two formulations were tested: Singulair® granules (4 mg), and Actavis® chewable tablets (5 mg) which were crushed prior to mixing (following reported practices (7)). For the direct administration scenario, formulations were tested in the simulated GI fluids without prior mixing with a vehicle. For the mixing with vehicles scenario, each sample was prepared by addition of the formulation to milk (25 mL; as previously investigated (Chapter 4)), applesauce (15 g) or formula (5 mL), followed by mixing with a stainless-steel spatula. Mixing with formula was performed only for the Singulair® granules to mimic the *in vivo* study dosing scenario (15).

2.2.3 Biorelevant *in vitro* dissolution studies

Dissolution studies were performed with a mini-paddle apparatus (Agilent Technologies 708-DS apparatus configured with TruAlign 200 mL vessels and electropolished stainless steel mini-paddles; Agilent, USA). Experiments were conducted at 37 ^{o}C, and agitation rate was set to 50 revolutions per minute (rpm). A two-stage approach was followed: gastric conditions were simulated for 1 h (Pi-

FaSSGF pH 1.6; total volume with sample: 100 mL), followed by intestinal simulated conditions (FaSSIF-V2 pH 6.5 or Pi-FeSSIF pH 5.8; final volume: 200 mL), for 3 h. Sample collection took place at 5, 15, 30, 45, 60, 75, 90, 120, 180 and 240 min. 2 mL samples were withdrawn (with volume replacement with the corresponding media), using a 2 mL glass syringe (Fortuna Optima® fitted with a stainless tubing) through a cannula fitted with a full flow filter (10 µm). All experiments were performed without direct light exposure to avoid photodegradation of montelukast (19). After collection, samples were filtered through a GF/D filter (2.7 µm), treated, placed into amber HPLC vials and injected into the HPLC. Treatment was as follows: 1000 µL of acetonitrile were added to 500 µL of the filtered sample, the mixture was vortexed (HTZ, UK) for 1 min, centrifuged (8000 rpm, 15 min, 4 ^{o}C) (Beckman Coulter J2-MC centrifuge, UK) and the supernatant was filtered through a RC filter (0.45 µm). The pH of the media was measured at the end of each experiment.

The effect of different administration scenarios on drug dissolution was investigated by varying the mode of the introduction of the formulation in the simulated gastric fluid in the dissolution vessel: direct administration of the formulation or administration of the formulation after mixing with drinks (formula and milk) or soft food (applesauce). These vehicles were selected based on their impact on the dissolution of montelukast (Chapter 4) and/or to mimic the *in vivo* studies performed in infants (14, 15, 17, 20).

All experiments were performed in triplicate. Fresh calibration curves (concentration range: 0.5 – 60 µg/mL) were prepared in the corresponding media, by appropriate dilution of a 1000 µg/mL stock solution of montelukast analytical standard in methanol. Results were expressed as mean percentage (%) drug dissolved ± standard deviation (S.D.) at the given sampling time.

2.2.4 Chromatographic conditions for drug analysis

The chromatographic method used for quantification of montelukast was a modification of the method by Raju NK *et al* (21). Drug quantification was performed with HPLC with ultraviolet (UV) detection (Agilent HPLC system 1100/1200 series; Agilent, USA), using a C_{18} column (RP Agilent Eclipse XDB, 250

mm x 4.6 mm, 5 µm particle size), and ammonium acetate buffer pH 5.5 (A) and methanol (B) as mobile phase, delivered on a linear gradient. The selected gradient started with 10 % of solvent B, which was increased to 50 % within 2 min, and 90 % within 4 min; at 11.30 min, the initial conditions of analysis were re-established. Injection volume was 100 µL, flow rate was 1 mL min^{-1}, run time was 12.30 min, detection wavelength was 284 nm, and column temperature was 20 ^{o}C.

2.2.5 Data analysis and calculations

2.2.5.1 In vitro data analysis and calculations

The linear trapezoidal method was used to calculate the area under the curve of each *in vitro* % drug dissolved over 4 h profile ($AUC_{0\text{-}4h}$ *in vitro*). One-way analysis of variance (ANOVA) with a post-hoc Tukey Honest Significant Difference (HSD) test was conducted to investigate differences in the $AUC_{0\text{-}4h}$ *in vitro* calculated from the dissolution studies, after direct administration of formulation and after mixing the formulation with the different vehicles ($p < 0.05$ noting significance level). *T*-test analysis was used to compare experimental results under fasted gastric conditions, followed by fasted or fed intestinal conditions (represented as Pi-FaSSGF/FASSIF-V2 and Pi-FaSSGF/Pi-FeSSIF, respectively) (significance $p < 0.05$). Analyses were performed with GraphPad Prism® v.7 software (USA).

2.2.5.2 In vivo data analysis and calculations

Published data of plasma concentration profiles of Singulair® granules (4 mg) co-administered to different infant subgroups with formula or applesauce (formula: 1 to 3 months; applesauce: 3 to 6 months and 6 to 24 months) were digitalised with WebPlotDigitalizer® v4.1 software (USA) (14, 15, 17, 22).

The corresponding *in vivo* drug absorption profiles were obtained after deconvolution of the oral data using the Wagner-Nelson equation (Eq. 5.1) (Excel, Microsoft®) (23).

$$\%\ absorbed = \frac{A(t)}{A(\infty)} x\ 100 = \frac{A(t)+k\int_{\tau=0}^{t} A(\tau)d\tau}{k\int_{\tau=0}^{\infty} A(\tau)d\tau} x\ 100 \qquad \text{(Eq. 5.1)}$$

where, $A(t)$ is the amount of drug in the system at time t and k is the first order elimination rate constant (23). The elimination rate constant was obtained from the slope of the terminal logarithmic concentrations of the *in vivo* montelukast oral data.

The linear trapezoidal method was used to calculate the area under the curve of each *in vivo* % drug absorbed over 4 h profile ($AUC_{0\text{-}4h}$ *in vivo*).

2.2.5.3 In vitro/in vivo relationship

An *in vitro–in vivo* relationship for Singulair® granules (4 mg) was investigated by comparing the *in vitro* dissolution ($AUC_{0\text{-}4h}$ *in vitro*) and the *in vivo* absorption data ($AUC_{0\text{-}4h}$ *in vivo*). Average differences between the obtained $AUC_{0\text{-}4h}$ *in vitro* and the $AUC_{0\text{-}4h}$ *in vivo* of the different subgroups were expressed as a ratio (%) ($AUC_{0\text{-}4h}$ *in vitro*/$AUC_{0\text{-}4h}$ *in vivo* x 100). For evaluation of the results, ratios lower than 100 % indicate that $AUC_{0\text{-}4h}$ *in vitro* was lower than the $AUC_{0\text{-}4h}$ *in vivo* and higher values represent the opposite. To denote relevant discrepancies between the $AUC_{0\text{-}4h}$ *in vitro* and $AUC_{0\text{-}4h}$ *in vivo*, reference points corresponding to ratios of 80 and 125% were used. Mean ratios falling inside this reference range were estimated to represent an *in vitro-in vivo* relationship, whereas when mean ratios were outside the reference range *in vitro* dissolution results were deemed not related to *in vivo* drug performance.

3. Results and discussion

3.1 Biorelevant *in vitro* drug dissolution studies for the assessment of the impact of medicine co-administration with food and drinks

Dissolution of montelukast from both formulations in the administration scenarios tested is presented in Figure 5.1. In gastric conditions (Pi-FaSSGF), dissolution of montelukast was higher when the formulations were mixed with milk, in comparison to direct administration and when mixed with applesauce. In intestinal conditions, differences in drug dissolution were observed for both formulations when testing under fasted or fed conditions (FaSSIF-V2 pH 6.5 or Pi-FeSSIF pH 5.8). These are probably attributed to an increase in drug solubilisation (drug solubility = 8 µg/mL and 53 µg/mL in FaSSIF-V2 and Pi-FeSSIF, respectively) due to the presence of a

higher concentration of bile salts and lecithin in the fed intestinal simulated fluid, as shown in solubility studies of montelukast in different paediatric media (12, 18, 24). In addition, the vehicle-impact on drug dissolution varied depending on the vehicles used for co-administration and the formulation tested. For example, when both formulations were mixed with applesauce, the impact of testing under fed intestinal conditions was higher for the crushed chewable tablets than for the granules.

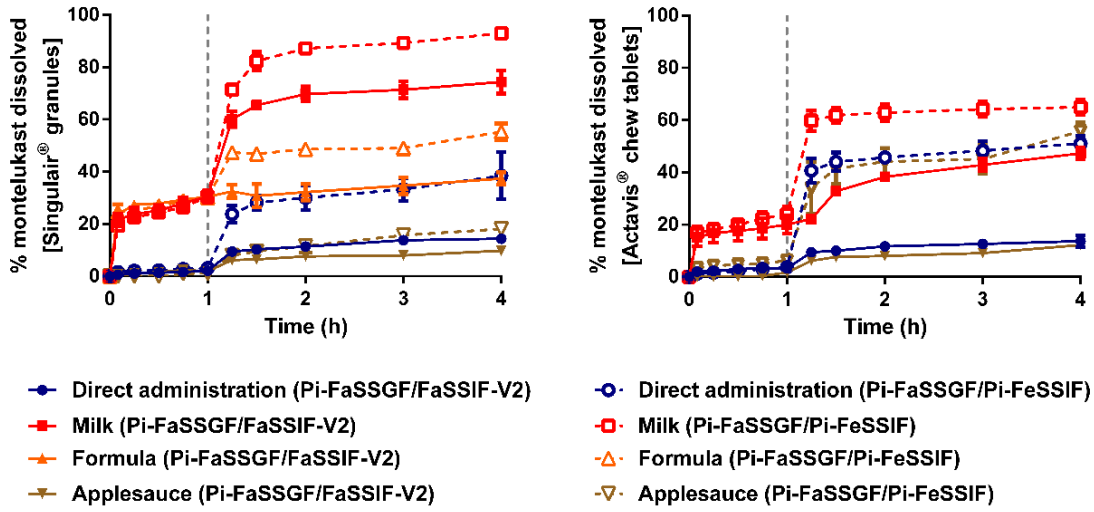


Figure 5.1. Mean % montelukast dissolved (± S.D.) from Singulair® granules and Actavis® chewable tablets after direct introduction of the formulation and mixing with selected vehicles, under fasted gastric conditions, followed by fasted (full lines) or fed (dashed lines) intestinal conditions. Dotted vertical lines represent the time of medium change.

Comparison of the $AUC_{0\text{-}4h}$ *in vitro* of the dissolution profiles (4 h) is presented in Figure 5.2. Results of the $AUC_{0\text{-}4h}$ *in vitro* confirmed that dissolution of montelukast from the two formulations tested was significantly affected by co-administration with vehicles, compared to the direct administration scenario. The $AUC_{0\text{-}4h}$ *in vitro* was also shown to be significantly higher when testing under fed state intestinal conditions in comparison to the fasted state.

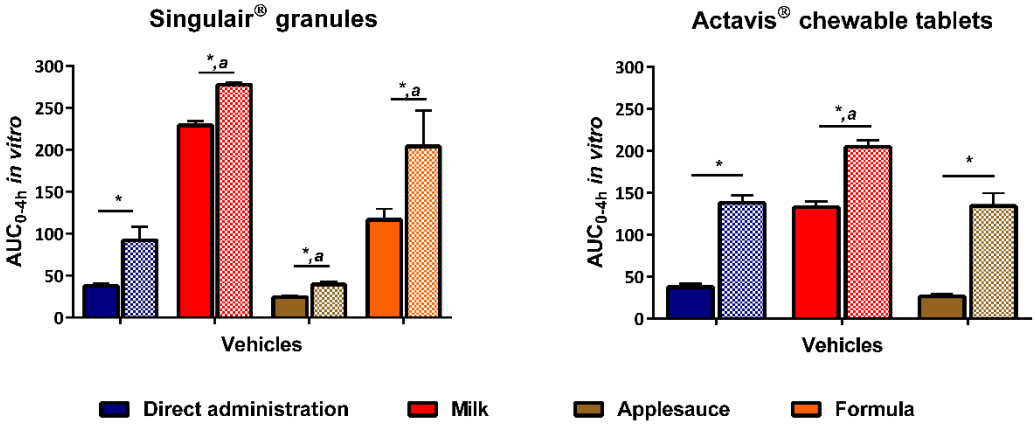


Figure 5.2. $AUC_{0\text{-}4h}$ *in vitro* (% dissolved*h) of montelukast dissolution profiles after direct administration of formulation and after mixing with the vehicles. *a* denotes statistical difference between direct administration (blue bars) and co-administration with vehicles (other colours); * denotes a statistical difference on drug dissolution between testing under fasted gastric conditions, followed by fasted (dashed bar) or fed (full bar) intestinal conditions ($p < 0.05$).

For Singulair® granules, the $AUC_{0\text{-}4h}$ *in vitro* of the direct administration of formulation scenario was significantly lower compared to the co-administration with drinks (milk and formula), and significantly higher than the co-administration with applesauce. Drug dissolution (4 h) was higher when the formulation was co-administered with milk (74.3 and 93.0 % drug dissolved in Pi-FaSSGF/FaSSIF-V2 and Pi-FaSSGF/Pi-FeSSIF, respectively), than when mixed with formula (% drug dissolved = 37.4 (Pi-FaSSGF/FaSSIF-V2) and 55.3 (Pi-FaSSGF/Pi-FeSSIF)). These results confirm that vehicles of the same subtype (*i.e.* dairy drinks) can have different effects on drug dissolution, in accordance with what was observed in Chapter 4 and previous studies (20, 25, 26). The lower dissolution of montelukast observed when the granules were mixed with formula compared to the drug dissolution when mixed with milk, relates to the differences in the solubility of montelukast in the two vehicles (milk: 13.3 mg/mL; formula: 12.0 mg/mL) (Chapter 2). It can be hypothesised that these differences were accentuated by the use of different volumes of the two drinks mixed with the formulation (15 mL milk and 5 mL formula). This is of particular importance considering that the recommendations for medicine co-administration with drinks/soft foods often do not specify the volume of vehicle to use (7). These results indicate the risk of unspecific recommendations for vehicle choice and volume, and further confirm the importance of the FDA draft guidance on vehicle selection and *in vitro* methods for product

quality assessment (9). The lowest % drug dissolution (4 h) was observed for the mixing with applesauce scenario (% drug dissolved = 9.8 (Pi-FaSSGF/FaSSIF-V2) and 18.1 (Pi-FaSSGF/Pi-FeSSIF)). As mentioned in Chapter 4, it is possible that this relates to the presence of starch in the composition of applesauce, which forms a net gel around the formulation and negatively affects drug release and dissolution (27).

The $AUC_{0\text{-}4h}$ *in vitro* for the crushed Actavis® chewable tablets mixed with applesauce was not significantly different from the direct introduction scenario, whereas a higher $AUC_{0\text{-}4h}$ *in vitro* was observed after mixing with milk (Figure 5.2). The higher drug dissolution when the formulation was mixed with milk is probably related to the higher drug solubilisation in milk, due to the high drug affinity for protein and fat globules in milk, as well as the higher pH and buffer capacity of this vehicle (Chapter 3)(24, 28).

Overall, it was observed that co-administration with food and drink vehicles significantly affects the dissolution of montelukast from both formulations. Results showed the influence of drug ionisation and solubility (*e.g.* higher % montelukast dissolved when formulations were mixed with milk), vehicle viscosity (*e.g.* higher viscosity of applesauce hinders the dissolution of the Singulair® granules), and alteration of formulation factors (granules and crushed chewable tablets displayed different dissolution behaviour when mixed with applesauce), on drug dissolution behaviour. In addition, simulated intestinal prandial conditions were shown to affect drug dissolution behaviour, with higher % drug dissolved (4 h) achieved when testing under Pi-FaSSGF/Pi-FeSSIF conditions. These results indicate that the impact of the practice of medicine co-administration with food and drinks will be higher if the vehicle used triggers a food effect *in vivo* or if medicine co-administration with vehicles is performed under fed conditions.

PK parameters will influence the extent of the vehicle-impact on drug dissolution and, consequently, drug behaviour and clinical outcomes. One of these parameters is the half-life of the drug, which will influence the C_{max} achieved. In this study, montelukast was chosen as a proof-of-concept molecule to understand the possible vehicle-impact on dissolution of a poorly soluble drug. It is a BCS class II drug, with a half-life of 4 h, which should be administered once-daily (12, 13, 15). The possible

vehicle-impact on drug dissolution may be significant in cases where drug has low permeability, low dissolution and short half-life (< 120 min) or if a fast onset therapeutic action is required. Vehicles that slow down drug dissolution might cause issues *in vivo*, because the drug can be metabolised and/or eliminated before it reaches therapeutically relevant systemic concentrations. For example, the C_{max} of a high-permeability and short half-life drug such as ibuprofen can be sensitive to the dissolution profile, as this drug requires frequent administration in order to maintain blood concentration levels within a therapeutically effective concentration range (29, 30). Vehicles that cause an increase in drug dissolution rate compared to the rate of absorption (limited by permeability restrictions) might be problematic if the drug achieves higher concentrations in the GI lumen than its equilibrium solubility, as this might lead to precipitation (31). Absorption is a complicated process and other GI physiological parameters might play a role, such as GI transit rates and volumes (31). Thus, the influence of these parameters should also be considered during evaluation of a possible vehicle-effect and could be captured if evaluated in a physiologically based pharmacokinetic model.

3.2 *In vivo* drug absorption

In published *in vivo* studies of Singulair® granules (4 mg) administered to infant patients, medicine administration was conducted by mixing the formulation with different vehicles: formula (5 mL) for the subgroup 1 to 3 months, and applesauce (15 g) to infants from 3 to 24 months (two subgroups: 3 to 6 and 6 to 24 months). However, the prandial state of the patients in these studies was not disclosed and no significant vehicle-induced differences on drug behaviour were considered (14, 15, 17, 22).

PK parameters of montelukast C_{max} and $AUC_{0\text{-}24\ h}$ after the administration of the 4 mg dose to infants of 1 to 3 months were higher and more variable than for older infants (3 to 24 months) (14, 15, 17). The higher systemic exposure in the younger subgroup when given the dose of montelukast was attributed to their smaller body weight, and to the levels of CYP3A4, which are only about 30 to 40 % of adult levels in ages younger than 3 to 12 months (15).

The *in vivo* % absorbed profiles of montelukast after administration of Singulair® granules, in the different subgroups of infants (calculated from the Wagner-Nelson equation of the plasma profiles (14, 15, 17, 22)), are shown in Figure 5.3.

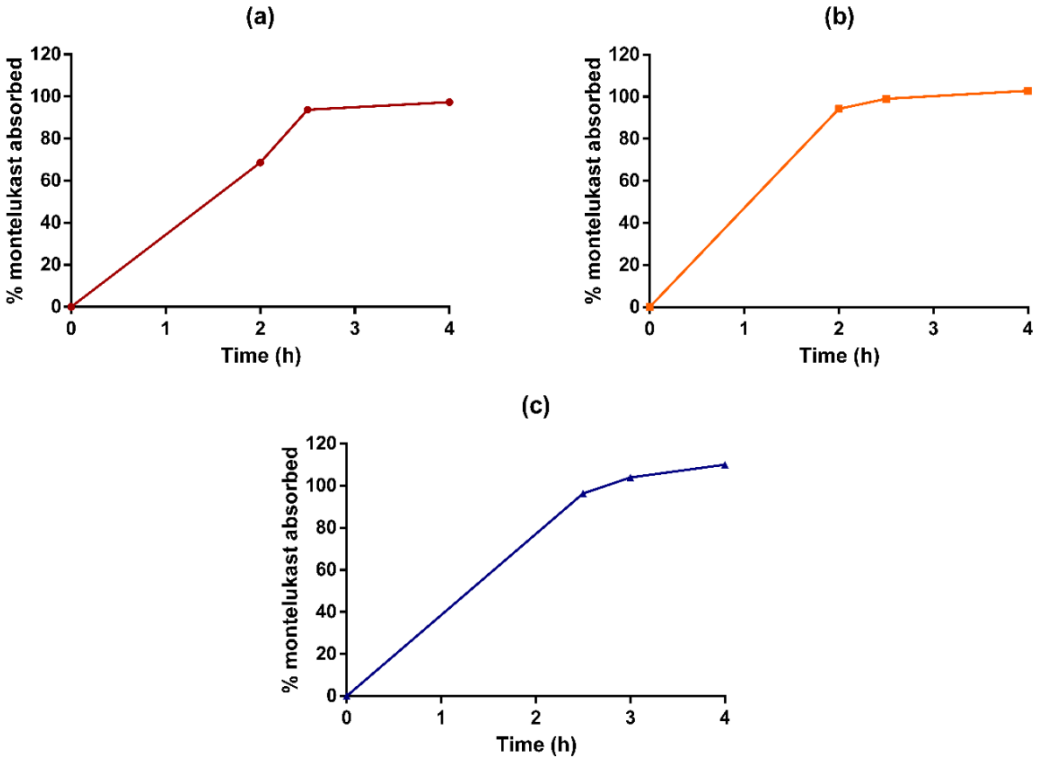


Figure 5.3. % of montelukast absorbed *in vivo* after administration of Singulair® granules (4 mg) to: (a) 1 to 3 months infants with formula (15); (b) 3 to 6 months infants with applesauce (14); and (c) 6 to 12 months infants with applesauce (17). The % absorbed was calculated with the Wagner–Nelson equation.

3.3 *In vitro-in vivo* relationships for Singulair® granules

The ratios between the $AUC_{0\text{-}4h}$ *in vitro* and the $AUC_{0\text{-}4h}$ *in vivo* are presented in Figure 5.4. The ratios were calculated from the $AUC_{0\text{-}4\ h}$ *in vitro* of the *in vitro* dissolution profiles of Singulair® granules directly administered or mixed with milk, formula or applesauce, under fasted gastric conditions followed by fasted or fed intestinal conditions, and the $AUC_{0\text{-}4\ h}$ *in vivo* in infants (3 subgroups: 1 to 3 months, 3 to 6 months and 6 to 24 months).

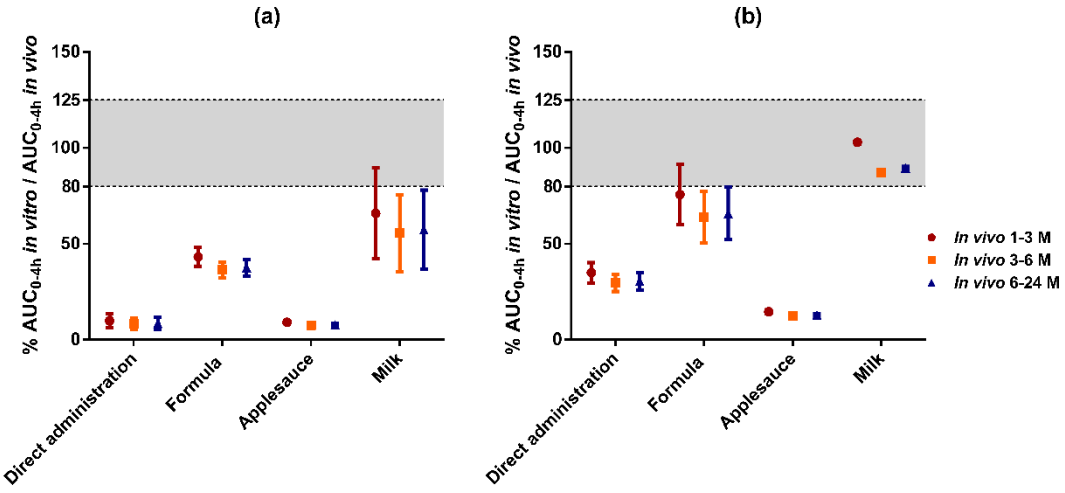


Figure 5.4. Ratio (%) between each $AUC_{0\text{-}4h}$ *in vitro* and $AUC_{0\text{-}4h}$ *in vivo* ($AUC_{0\text{-}4h}$ *in vitro*/$AUC_{0\text{-}4h}$ *in vivo* x 100) for: (a) *in vitro* fasted gastric followed by fasted intestinal conditions; and (b) *in vitro* fasted gastric followed by fed intestinal conditions. Grey area represents the range criteria (80 – 125 %) set for prediction of *in vivo* drug performance.

In the cases of direct introduction of Singulair® granules and mixing with applesauce, the *in vitro* drug dissolution was much slower than the *in vivo* absorption of montelukast, in all subgroups (% $AUC_{0\text{-}4h}$ *in vitro*/$AUC_{0\text{-}4h}$ *in vivo* ratio lower than 80%). In these cases, as *in vitro* drug dissolution was slower than *in vivo* absorption, it might be hypothesised that the *in vitro* test must be improved (1).

For the mixing of Singulair® granules with formula scenario, when testing under fasted gastric conditions followed by fed intestinal conditions, the $AUC_{0\text{-}4h}$ *in vitro*/$AUC_{0\text{-}4h}$ *in vivo* ratio fell inside the 80 – 125 % limits for one of the subgroups tested *in vivo* (1 to 3 months old), even though it was under the limits for the other subgroups. Conversely, the *in vitro-in vivo* ratio was lower than the 80 % limit for all subgroups when testing under fasted gastric conditions followed by fasted intestinal conditions. These results indicate that the biorelevant *in vitro* dissolution test under fasted gastric conditions followed by fed intestinal conditions gives a good prediction of the *in vivo* product performance for the 1 to 3 months subgroup.

For the Singulair® granules mixed with milk, when testing under fasted gastric conditions followed by fed intestinal conditions and comparing to *in vivo* results in infants from all subgroups, the $AUC_{0\text{-}4h}$ *in vitro*/$AUC_{0\text{-}4h}$ *in vivo* ratio fell inside the 80 – 125 % limits. However, under *in vitro* fasted gastric conditions followed by fasted intestinal conditions, the $AUC_{0\text{-}4h}$ *in vitro*/$AUC_{0\text{-}4h}$ *in vivo* ratio only fell inside

the 80 – 125 % limits when using the *in vivo* data from the studies conducted in infants from 1 to 3 months old. These results indicate that the biorelevant *in vitro* dissolution test (fasted gastric conditions followed by fed intestinal conditions) using milk gives the best prediction of the *in vivo* product performance for all the tested subgroups. A good relationship was also found between the *in vivo* performance, for the 1 to 3 months subgroup, and the *in vitro* setup when using milk and testing under fasted gastric conditions followed by fasted intestinal conditions.

Overall, even though in the *in vivo* studies the prandial state of the infants is not evident, results suggest that these were likely performed in the fed state or that the practice of medicine co-administration with food and drinks might trigger fed state conditions *in vivo*. Nevertheless, further investigations would be needed to confirm and refine the dissolution testing parameters (*e.g.* media volume and composition, and dissolution hydrodynamics), and ensure the establishment of predictive, physiologically relevant methodology (1, 2). To this extent, characterisation of paediatric GI contents of different age groups *in vivo* is warranted for validation of paediatric biorelevant media and to allow the establishment of certainty and confidence in these paediatric biopharmaceutical methods.

4. Conclusions

The practice of mixing medicines with food and drinks may affect drug behaviour, leading to potential clinical implications. As emphasized in the recent FDA draft guidance on the use of vehicles for drug administration, this potential impact should be assessed during formulation development/evaluation by using different biopharmaceutical tools. In this study,

Dissolution of montelukast was significantly affected when mixing the tested formulation with vehicles in comparison to the scenario direct administration of formulation. Moreover, drug dissolution was significantly higher when testing under fed state intestinal conditions in comparison to the fasted state.

The biorelevant *in vitro* dissolution test (fasted gastric conditions followed by fed intestinal conditions) of the Singulair® granules mixed with milk scenario led to the best prediction of the *in vivo* drug performance in infant subgroups (1 to 3 months, 3

to 6 months and 6 to 24 months). Moreover, results from this study suggest that they were performed in the fed state or that the practice of medicine co-administration with food and drinks might have triggered fed state conditions *in vivo*.

The good relationship between the *in vitro* drug dissolution and *in vivo* absorption demonstrates the potential utility of biorelevant *in vitro* dissolution testing to understand the potential impact of co-administration of paediatric medicines with vehicles on drug performance. Ultimately, the use of *in vitro* tools like the one described could help understand the impact of this administration practice and avoid potential clinical implications.

References

1. Cardot J, Davit B. In vitro–in vivo correlations: tricks and traps. AAPS J. 2012;14(3):491-9.

2. Mercuri A, Fares R, Bresciani M, Fotaki N. An in vitro–in vivo correlation study for nifedipine immediate release capsules administered with water, alcoholic and non-alcoholic beverages: Impact of in vitro dissolution media and hydrodynamics. Int J Pharm. 2016;499(1-2):330-42.

3. Kostewicz ES, Abrahamsson B, Brewster M, Brouwers J, Butler J, Carlert S, et al. In vitro models for the prediction of in vivo performance of oral dosage forms. Eur J Pharm Sci. 2014;57:342-66.

4. Fotaki N, Vertzoni M. Biorelevant dissolution methods and their applications in in vitro-in vivo correlations for oral formulations. Open Drug Deliv J. 2010;4(2):2-13.

5. Mercuri A, Pagliari M, Baxevanis F, Fares R, Fotaki N. Understanding and predicting the impact of critical dissolution variables for nifedipine immediate release capsules by multivariate data analysis. Int J Pharm. 2017;518(1-2):41-9.

6. Batchelor HK, Fotaki N, Klein S. Paediatric oral biopharmaceutics: key considerations and current challenges. Adv Drug Deliv Rev. 2014;73:102-26.

7. Martir J, Flanagan T, Mann J, Fotaki N. Recommended strategies for the oral administration of paediatric medicines with food and drinks in the context of their biopharmaceutical properties: a review. J Pharm Pharmacol. 2017;69(4):384-97.

8. Orlu M, Salunke S, Tuleu C. Paediatric Pharmaceutics—The Science of Formulating Medicines for Children. Pharmaceutical Formulation: The Science and Technology of Dosage Forms: The Royal Society of Chemistry; 2018. p. 258-87.

9. Food and Drug Administration. Center for Drug Evaluation and Research, Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments - Draft Guidance for Industry. 2018. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM614401.pdf. Accessed 6 October 2018.

10. Ernest TB, Elder DP, Martini LG, Roberts M, Ford JL. Developing paediatric medicines: identifying the needs and recognizing the challenges. J Pharm Pharmacol. 2007;59(8):1043-55.

11. Batchelor H, Kaukonen AM, Klein S, Davit B, Ju R, Ternik R, et al. Food effects in paediatric medicines development for products co-administered with food. Int J Pharm. 2018;536(2):530-5.

12. Okumu A, DiMaso M, Löbenberg R. Dynamic dissolution testing to establish in vitro/in vivo correlations for montelukast sodium, a poorly soluble drug. Pharm Res. 2008;25(12):2778-85.

13. BNF for Children (BNFC) 2016-2017: Royal Pharmaceutical Society of Great Britain, British Medical Association, Pharmaceutical Press; 2017.

14. Knorr B, Maganti L, Ramakrishnan R, Tozzi CA, Migoya E, Kearns G. Pharmacokinetics and safety of montelukast in children aged 3 to 6 months. J Clin Pharmacol. 2006;46(6):620-7.

15. Kearns GL, Lu S, Maganti L, Li XS, Migoya E, Ahmed T, et al. Pharmacokinetics and safety of montelukast oral granules in children 1 to 3 months of age with bronchiolitis. J Clin Pharmacol. 2008;48(4):502-11.

16. Knorr B, Holland S, Schwartz J, Rogers JD, Reiss T. Clinical pharmacology of montelukast. Clin Exp Allergy. 2001;1(3):254-60.

17. Migoya E, Kearns GL, Hartford A, Zhao J, van Adelsberg J, Tozzi CA, et al. Pharmacokinetics of montelukast in asthmatic patients 6 to 24 months old. J Clin Pharmacol. 2004;44(5):487-94.

18. Maharaj AR, Edginton AN, Fotaki N. Assessment of age-related changes in pediatric gastrointestinal solubility. Pharm Res. 2016;33(1):52-71.

19. Smith GA, Rawls CM, Kunka RL. An automated method for the determination of montelukast in human plasma using dual-column HPLC analysis and peak height summation of the parent compound and its photodegradation product. Pharml Res. 2004;21(9):1539-44.

20. Martir J, Flanagan T, Mann J, Fotaki N. Effect of co-administration of foods and drinks on the dissolution of paediatric formulations - case study montelukast. 2018. Abstract from AAPS PharmSci 360, Washington DC, USA. .

21. Raju KN, Swamy TG, Rao AL. Development and validation of RP-HPLC method for the determination of montelukast sodium in bulk and in pharmaceutical formulation. J Pharm Chem Biol Sci. 2011;1(1):12-6.

22. Jones HM, Chen Y, Gibson C, Heimbach T, Parrott N, Peters SA, et al. Physiologically based pharmacokinetic modeling in drug discovery and development: a pharmaceutical industry perspective. Clin Pharmacol Ther. 2015;97(3):247-62.

23. Wagner JG, Nelson E. Kinetic analysis of blood levels and urinary excretion in the absorptive phase after single doses of drug. J Pharm Sci. 1964;53(11):1392-403.

24. Guimarães Sa Correia M, Maharaj A, Edginton A, Vertzoni M, Fotaki N. Understanding the impact of age-related changes in paediatric gastrointestinal solubility by multivariate data analysis. 2018. Abstract from AAPS PharmSci 360, Washington DC, USA.

25. Martir J, Flanagan T, Mann J, Fotaki N. Effect of co-administration of foods and drinks on the dissolution of paediatric formulations – case study mesalazine. 2018. Abstract from AAPS PharmSci 360, Washington DC, USA. .

26. Wells KA, Losin WG. In vitro stability, potency, and dissolution of duloxetine enteric-coated pellets after exposure to applesauce, apple juice, and chocolate pudding. Clin Ther. 2008;30(7):1300-8.

27. Manrique YJ, Lee DJ, Islam F, Nissen LM, Cichero JA, Stokes JR, et al. Crushed tablets: does the administration of food vehicles and thickened fluids to aid medication swallowing alter drug release? J Pharm Pharm Sci. 2014;17(2):207-19.

28. Martir J, Flanagan T, Mann J, Fotaki N. Impact of co-administration of food and drink vehicles on the solubility of poorly soluble paediatric drugs. 2017. Abstract from AAPS annual meeting, San Diego, USA.

29. Sood A, Panchagnula R. Design of controlled release delivery systems using a modified pharmacokinetic approach: a case study for drugs having a short elimination half-life and a narrow therapeutic index. Int J Pharm. 2003;261(1-2):27-41.

30. Bramlage P, Goldis A. Bioequivalence study of three ibuprofen formulations after single dose administration in healthy volunteers. BMC pharmacology. 2008;8(1):18.

31. Sugano K, Terada K. Rate-and extent-limiting factors of oral drug absorption: theory and applications. J Pharm Sci. 2015;104(9):2777-88.

Chapter 6: BCS-based biowaivers: extension to paediatrics

Abstract

Objectives: The aims of this study were to: (i.) identify compounds which would change drug solubility classification in the paediatric population, and (ii.) to assess the risk of extending BCS-based biowaiver criteria into paediatric products of these compounds.

Methods: Amoxicillin, prednisolone and amlodipine were selected as the model compounds. Dissolution studies of IR formulations of these compounds were conducted with USP II (paddle) and mini-paddle apparatus, in media of three pHs (pH 1.2, 4.5 and 6.8). Three dissolution setups were tested: (1) 'typical' BCS-based biowaiver conditions, (2) setup derived from BE study protocols (volume: 250 mL), and (3) extrapolation of a volume representative of the paediatric population (50 mL).

Key findings: Results revealed that only the 5 mg prednisolone and the 10 mg amlodipine tablets (Istin® and Teva® but not Sandoz®) would qualify for a biowaiver status, under all setup scenarios tested. In view of these results, it was shown that extension of regulated BCS-based biowaiver criteria for paediatric application is not straightforward and cannot be based on direct assumptions (*i.e.* simple scaling down). It was further shown that BCS-based biowaiver criteria should not be applied when there is a risk of a change of the drug solubility class, from the adult to paediatric populations.

Conclusions: Drug solubility considerations for adult BCS might not directly apply to paediatric subpopulations and extrapolation of BCS-based criteria into paediatric formulations should be undertaken with caution. A deeper knowledge of the paediatric GI environment is still lacking and would assist in refining the biopharmaceutical tools needed to appropriately evaluate formulation performance across age groups. This would not only be of great scientific interest but also potentially reduce the number of clinical studies required and speed up formulation development.

1. Introduction

Biopharmaceutical tools are extensively used in the design and development of pharmaceutical formulations, namely in risk assessment and optimisation of formulation performance. The application of these tools in paediatric medicines is currently still limited (1). Despite the increased effort put into improving the safety and effectiveness of paediatric medicines, development of medicines for this population is hindered by ethical considerations and technical constraints (*e.g.* physiological and anatomical changes), leading to knowledge gaps (2-5). Consequently, the tools currently used to undertake biopharmaceutical risk assessment of paediatric formulations are based on adult tests, addressing adult physiology and anatomy (1). However, the paediatric population has distinct needs with respect to formulation design and performance and thus adult formulations may not be suitable. Due to the challenges faced during paediatric medicine development, regulations have been reformed to address paediatric drug development in parallel to adult formulations (2, 3). Preliminary *enabling* formulations might be used in early paediatric studies, followed by a confirmatory study in which better-designed market formulations are introduced (6). Supportive clinical studies (*e.g.* relative bioavailability (BA) or bioequivalence (BE)) or *in vitro* techniques may then be used to establish the bridge from adult and/or enabling formulations to the final paediatric formulation.

From a regulatory perspective, during drug development a BE study should be conducted for a new formulation that has not been tested in efficacy trials. Pharmacokinetic (PK) parameters of two formulations (*i.e.* area under the curve (AUC), maximum plasma concentration (C_{max}) and time to maximum concentration (T_{max})) are compared; if the rate and extent of drug absorption fall within predefined limits, comparable *in vivo* drug exposure is ensured. BE studies of paediatric products are currently conducted in adults, with subsequent extrapolation to the target age group and a dose determination/confirmation study (6).

Bioequivalence studies may be exempted if *in vitro* dissolution testing can be used as a surrogate to adequately predict the *in vivo* drug performance (biowaivers). The biopharmaceutics classification system (BCS) is a scientific tool which categorises drugs according to their (high or low) solubility and intestinal permeability (7). This

system has been adopted as a very useful tool for *in vivo* drug design and development, particularly in terms of regulatory standards. BCS-based biowaivers have become an important and cost-saving tool in the development of new medicines, formulation bridging and generic drug approval. When combined with *in vitro* dissolution, BCS-based biowaivers consider the three major factors that govern the rate and extent of oral drug absorption from immediate release (IR) dosage forms. An IR oral solid formulation (test product) is eligible for a BCS-based biowaiver if the drug satisfies solubility criterion (high solubility; BCS class I/III), and the dosage form is pharmaceutically equivalent to the reference product (8-10). BCS-based biowaiver criteria are detailed in regulatory guidance documents (8-10). In the USA, it is required that at least 85 % of the labelled amount of drug substance should dissolve from the product within 15 min (BCS class III drugs) or 30 min (BCS class I drugs), in 900 mL media (500 mL or less can be allowed with scientific justification) cross a pH range (pH 1.2, 4.5 and 6.8), using USP apparatus I (100 revolutions per minute [rpm]) or II (50 rpm or 75rpm, if justified). The time frame criterion for BCS class I drugs, is subdivided into *very rapidly* and *rapidly* dissolving products (time-limits of 15 and 30 min, respectively), in guidelines from the World Health Organisation (WHO) and the European Medicines Agency (EMA) (8-10). There are no equivalent guidance documents for paediatric products, and the relevance of the defined criteria in this population is unknown.

Currently, biowaiver decisions are based on the drug properties related to the adult population. However, a BCS-biowaiver approach for paediatric products would be beneficial towards producing age-appropriate medicines, whilst minimising/eliminating scientific regulatory risks. Potentially this could be explored if both the reference (*e.g.* adult formulation or enabling paediatric formulation) and test formulations are pharmaceutical equivalents exhibiting rapid and similar dissolution profiles.

The use of the BCS in paediatrics is limited due to several biopharmaceutical particularities regarding paediatric physiology and PK parameters, therefore BCS-based biowaivers are not feasible for this population (4, 11). These particularities include gastrointestinal (GI) pH and volumes, which can influence drug solubility and ionised fraction. Additionally, permeability changes occur as function of the relative size of the small intestine, weight gain and maturation of GI transporters

(*e.g.* P-glycoprotein) (3, 12). Thus, the role of BCS and biowaivers in paediatric medicine development is unclear (13, 14).

In this context, it is important to investigate the possible changes on the biopharmaceutical characteristics of the drug as a function of the different age groups. Age-related physiological and/or anatomical changes may be responsible for shifts in the BCS classification of a drug due to changes in its solubility and permeability classification (15). Recent studies have shown that a drug which exhibits a high dose/solubility ratio in adults (*i.e.* highly soluble drugs) might not show the same ratio in paediatric patients, and unfavourably shift into poorly soluble classification. Consequently, these drugs would not be eligible for BCS-based biowaivers among pediatric populations (15, 16).

The aims of this study were to assess the risk of extending the biowaiver criteria for IR formulations from adults to paediatrics, and to identify bioinequivalence risks when comparing the performance of different formulations in age-appropriate BCS-conditions. The biowaiver decision was then discussed not only in terms of the formal requirements set out in existent guidance, but also in the context of the risks associated with an incorrect biowaiver decision. Drugs were selected based on the identified risk of shifting into poorly soluble classification in the different paediatric age groups and, consequently, not being eligible for a BCS-based biowaiver. Amoxicillin, amlodipine and prednisolone were selected as the model compounds.

2. Materials and methods

2.1 Materials

Sodium hydroxide, 37 % hydrochloric acid, sodium chloride, glacial acetic acid, potassium dihydrogen phosphate, sodium acetate trihydrate and sodium phosphate anhydrous were purchased from Fisher Scientific (UK). Water was ultra-pure (Milli-Q) laboratory grade. Regenerated cellulose [RC] membrane filters (0.45 µm) were from Cronus® (UK). Amoxicillin trihydrate (98 %) was purchased from VWR (UK). Prednisolone (99 %) and amlodipine besylate (pharmaceutical secondary standard) were obtained from Sigma-Aldrich (UK). Details of the formulations used are presented in Table 6.1.

Table 6.1. Information of the formulations used in this study.

Drug	Formulation	Manufacturer	Dose (Batch)	Excipients
Amoxicillin (trihydrate)	Amoxil® capsules	GlaxoSmithKline plc (UK)	250 mg (2398) 500 mg (X54F)	Magnesium stearate E572, gelatine, erythrosine E127, titanium dioxide E171, indigotine E132, iron oxide yellow E172 and shellac E904
	Teva® capsules	Teva Pharmaceutical Industries Ltd (UK)	250 mg (AXABV0005) 500 mg (13753)	Croscarmellose sodium, magnesium stearate, sunset yellow E110, carmosine E122, brilliant blue E133, Quinoline Yellow E104, titanium dioxide E171, methyl parahydroxybenzoate and propyl parahydroxybenzoate
	Kent® capsules	Kent Pharmaceuticals Ltd (UK)	250 mg (13095) 500 mg (15768)	Magnesium stearate, maize starch, gelatine, erythrosine E127, quinoline Yellow E104, titanium dioxide E171, red iron oxide E172
Prednisolone	Pevanti® tablets	Mercury Pharma Ltd (UK)	5 mg (17K09A) 25 mg (17F25A)	Potato starch, lactose, talc, gelatine and magnesium stearate
	Actavis® tablets	Actavis Generics Ltd (UK)	5 mg (4F46) 25 mg (YK13)	Lactose monohydrate, pregelatinized starch, sodium starch glycolate type A, iron oxide yellow E172, iron oxide red E172, glycerol dibehenate, magnesium stearate
Amlodipine (besylate)	Istin® tablets	Pfizer Ltd (UK)	5 mg (2398) 10 mg (X54F)	Calcium hydrogen phosphate anhydrous, magnesium stearate, microcrystalline cellulose and sodium starch glycolate type A.
	Sandoz® tablets	Sandoz Ltd (UK)	5 mg (HM8397) 10 mg (HK5291)	Microcrystalline cellulose, anhydrous calcium hydrogen phosphate, sodium starch glycolate type A and magnesium stearate.
	Teva® tablets	Teva Pharmaceutical Industries Ltd (UK)	5 mg (0190317) 10 mg (7940517)	Microcrystalline cellulose, calcium hydrogen phosphate, sodium starch glycolate and magnesium stearate.

2.2 Methods

2.2.1 Drug and dose selection

Amoxicillin (trihydrate), prednisolone and amlodipine (besylate) were selected as the model compounds. They are included in the Model List of Essential Medicines for Children, with two dose strengths specified for each drug (17). Two doses (one paediatric and one adult) were selected for this study; these were: 250 and 500 mg for amoxicillin, 5 and 25 mg for prednisolone and 5 and 10 mg for amlodipine.

The BCS allows the classification of drugs as highly soluble when the highest drug dose (or dose unit, D_0) is soluble in 250 mL of an aqueous liquid at a relevant physiological pH range of 1.2 – 6.8 (7). According to this criterion, the three drugs (all doses) selected are classified as highly soluble drugs (18-20). The key factors that define drug dose unit (*i.e.* highest dose strength, initial gastric volume available (V_0) and drug solubility) have been shown to vary amongst the different populations (15, 16, 21). The paediatric D_0 of these drugs were estimated across the different paediatric age groups (average age in each subpopulation was used for the calculations; Table 6.2), using the following equation (Eq. 6.1) (15):

$$D_0 = \frac{(\text{Paediatric dose})/(\text{Paediatric reference volume})}{\text{Drug solubility}} \qquad \text{(Eq. 6.1)}$$

where, aqueous drug solubility data was obtained from the literature (22), and the reference volumes for paediatric groups were determined using the equation (Eq. 6.2):

$$Paediatric\ reference\ volume\ (mL) = \frac{\text{Weight (kg)}\ x\ 0.56}{40}\ x\ 250 \qquad \text{(Eq. 6.2)}$$

where, 0.56 mL/kg and 40 mL are estimates of fasted gastric fluids volumes in paediatrics (23) and adults (24), respectively, and 250 mL is the reference volume used in the BCS (8-10).

All drugs were shown to change D_0 (Table 6.2) and consequently BCS class, with a shift from high drug solubility classification in adults to low drug solubility classification (given by $D_0 > 1$ (4)) in certain paediatric age groups. The BCS-based biowaiver status claimed in adults may therefore not be safely extended to the paediatric population. Thus, these drugs were chosen as the model compounds for this study.

Table 6.2. Dose unit in different age groups from early infancy through to adulthood. High and low drug solubility classification are denoted by red ($D_0 > 1$) and black ($D_0 < 1$) colours, respectively. Paediatric reference volumes were calculated with the average weight of the age group (12).

Drug	Aqueous solubility (mg/mL) (22)	Dose strength (mg)	D_0				
			3 Years / V_0 = 54 mL	6 Years / V_0 = 79.2 mL	10 Years / V_0 = 121 mL	17 Years / V_0 = 245 mL	Adult / V_0 = 250 mL
Amoxicillin (trihydrate)	3.43	250	1.350	0.920	0.602	0.297	0.292
		500	2.699	1.841	1.205	0.595	0.583
Prednisolone	0.223	5	0.415	0.283	0.185	0.092	0.0897
		25	2.076	1.415	0.927	0.458	0.448
Amlodipine (besylate)	0.075	5	1.230	0.838	0.549	0.271	0.266
		10	2.459	1.677	1.098	0.542	0.531

(D_0 = dose unit; V_0 = gastric volume available)

2.2.2 *In vitro* dissolution studies

In vitro dissolution studies were conducted with USP II apparatus or mini-paddle apparatus (Agilent 708-DS Dissolution apparatus; Agilent, USA). For the mini-paddle setup, TruAlign 200 mL vessels and electropolished stainless steel mini-paddles were used (Agilent, USA). Experiments were conducted at 37 ± 0.5 ^{o}C in three media; simulated gastric fluid *sine pepsin* (SGF*sp*) pH 1.2, acetate buffer pH 4.5 and phosphate buffer pH 6.8 (25). Three different setups were developed for the assessment of formulation performance and equivalence, in dissolution conditions representative of both adults and paediatric populations (Figure 6.1). Setup 1 was conducted in USP II apparatus, using 900 mL of dissolution media and an agitation of 50 rpm (prednisolone and amlodipine) or 75 rpm (amoxicillin) (setup 1, old 'typical' BCS-based biowaiver conditions). Setup 2 was conducted in USP II apparatus, using 250 mL of media and an agitation rate of 50 rpm (prednisolone and amlodipine) or 75 rpm (amoxicillin) (setup 2, derived from BE study protocols that prescribe administration of a drug product to fasting human volunteers with a glass of water of 250 mL). Setup 3: was conducted in mini-paddle apparatus, using 50 mL of dissolution media and an agitation rate of 125 rpm (prednisolone and amlodipine) or 187.5 rpm (amoxicillin) (setup 3, where a 50 mL volume representative of the paediatric population was used). The agitation rate for setup 3 in the mini paddle

apparatus (125 or 187.5 rpm) was set based on the speed factor of 2.5 between paddle and mini-paddle hydrodynamics [*i.e.* Agitation rate mini-paddle = 2.5 * agitation rate paddle] to reflect the agitation rate used in the USP II apparatus (50 or 75 rpm, respectively) (26). Other requirements for granting the biowaiver status (*i.e.* pH range for testing and time frame limits for rapid dissolution of the formulations) were maintained for all setups, as per current regulations.

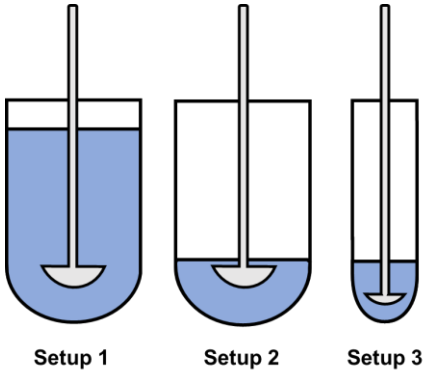


Figure 6.1. Schematic representation of the different dissolution setups tested: (1) 900 mL, USP II apparatus; (2) 250 mL, USP II apparatus; (3) 50 mL, mini-paddle apparatus.

For amoxicillin capsules, slow dissolution was observed when testing at 50 rpm in media of pH 4.5 and 6.8. To explore the dissolution performance of the drug products and investigate if there were experimental issues of coning, dissolution tests were performed with Amoxil® 250 and 500 mg capsules (reference product), in media of pH 4.5 and 6.8 at three agitation rate conditions; 50, 75 and 100 rpm. Two volumes were tested: 900 mL (setup 1) and 250 mL (setup 2).

Experiments were conducted for 60 min or 120 min, depending on whether complete dissolution was reached within 60 min. For amoxicillin testing, capsules were put in sinkers (Quality Lab Accessories LCC, USA). Sample collection took place at 5, 10, 15, 20, 30, 45, 60, 75, 90 and 120 min. 2 mL samples were withdrawn (with volume replacement) using a 2 mL glass syringe (Fortuna Optima® fitted with a stainless tubing) through a cannula (Quality Lab Accessories LCC, USA). Each sample was filtered with a RC filter (0.45 µm), and appropriately diluted prior to quantitative analysis. All experiments were performed in triplicate. Samples were analysed at 272 (amoxicillin), 246 (prednisolone) and 239 (amlodipine) nm, using an UV

spectrophotometer (Thermo Scientific Helios Gamma UV-Vis Spectrophotometer, Thermo Fisher Scientific, UK) equipped with a cuvette.

Drug quantification was performed based on calibration curves prepared in the corresponding media for each experiment. Freshly prepared standard solutions (concentration range: 5 – 120 μg/mL (amoxicillin) or 2 – 30 μg/mL (prednisolone and amlodipine)) were prepared by appropriate dilution of a 1000 μg/mL stock solution of the analytical standard in water (amoxicillin) or methanol (prednisolone and amlodipine). The interfering effect of formulation excipients on the maximum absorption of the compounds was deemed insignificant, after scanning and comparing the spectrum of each stock solution with the spectrum of a solution of same concentration of the dissolved dosage forms in water (amoxicillin) or methanol (prednisolone or amlodipine) (data not shown). Results were expressed as mean percentage (%) drug dissolved ± standard deviation (S.D.), at the given sampling time.

2.2.3 Treatment of dissolution data

To qualify for a BCS-based biowaiver, both the test product and reference should display a mean % drug dissolved above 85 % within 15 or 30 min, and similar *in vitro* dissolution characteristics, under all the defined conditions (*i.e.* agitation rate, pH range). When > 85% of the label amount of drug was dissolved in 15 min (for both test and reference products), the dissolution profiles were considered similar. If this was not the case, the similarity factor f_2 was estimated for comparison of dissolution profiles, by using the following equation (Eq. 6.3) (27):

$$f_2 = 50 \bullet \log\left(\frac{100}{\sqrt{1+\frac{\sum_{t=1}^{n}[\overline{R}(t)-\overline{T}(t)]^2}{n}}}\right) \qquad \text{(Eq. 6.3)}$$

where, n is the number of time points, $\overline{R}(t)$ is the mean percent of reference drug dissolved at time *t* after starting the study; and $\overline{T}(t)$ is the mean percent of test drug dissolved at time t.

DDsolver® software (an Add-In for Excel, Microsoft®) was used to determine the similarity factor f_2. The evaluation of the similarity factor was based on three

conditions: (i.) a minimum of three time points was used, (ii.) the time points used were the same for the two products compared, (iii.) not more than one mean value of ≥ 85% dissolved for any of the products was included in the analysis. The coefficient of variation was less than 20 % at early time points and less than 10% at other time points, thus allowing the use of mean values for evaluation of the similarity factor (8). Two dissolution profiles were considered similar when the f_2 value was ≥ 50 (27).

3. Results and discussion

3.1 Amoxicillin

Amoxicillin can be classified as a BCS class I drug, according to drug solubility and permeability studies (18). According to regulations for BCS-based biowaivers, dissolution studies should be performed with USP II paddle apparatus at 50 rpm. Amoxicillin capsules had a slow and incomplete dissolution when dissolution testing was performed at this agitation rate in media of pH 4.5 and 6.8. At an agitation rate of 75 rpm and 100 rpm, dissolution of amoxicillin from the Amoxil® capsules (reference product; 250 and 500 mg) was rapid and reached completion, with low variability between replicates. These results revealed that at lower agitation rate (50 rpm) a coning effect was taking place (Figure 6.2). Therefore, the dissolution tests for the amoxicillin capsules were performed at 75 rpm (setup 1 and 2 conditions) and 187.5 rpm (setup 3 conditions).

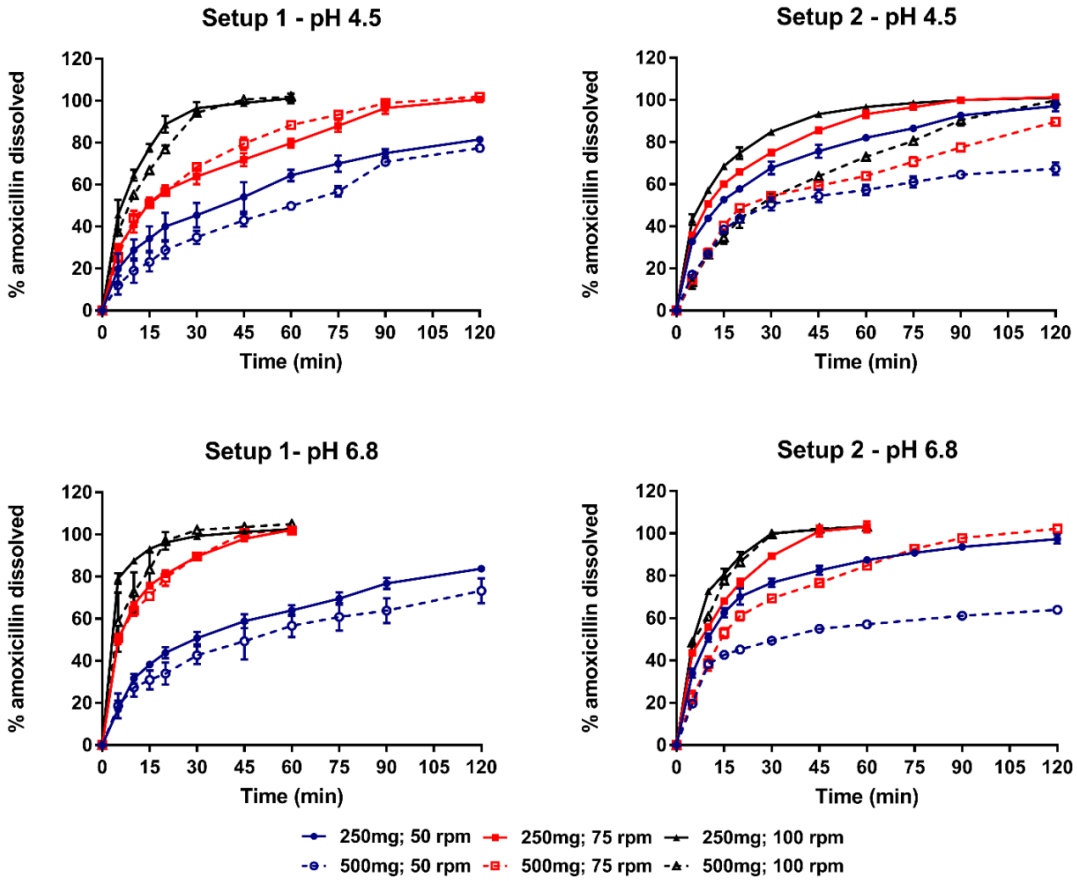


Figure 6.2. Mean % amoxicillin dissolved (± S.D.) from Amoxil® capsules 250 mg (full lines) and 500 mg (dashed lines), in acetate buffer pH 4.5 (top) and phosphate buffer pH 6.8 (bottom), under two testing scenarios: setup 1 (USP II apparatus, 900 mL) and setup 2 (USP II apparatus, 250 mL) (left and right panels, respectively). Three agitation rates were tested: 50 rpm (blue), 75 rpm (red) and 100 rpm (black).

Dissolution of amoxicillin from the formulations tested (reference: Amoxil®; test: Teva® and Kent®) is presented in Figure 6.3 and f_2 similarity factors estimated for comparison of the dissolution profiles in Table 6.3. For the 250 mg amoxicillin capsules, under setup 1 conditions at pH 1.2, more than 85 % of amoxicillin was dissolved from the tested formulations within 15 min. In the acetate (pH 4.5) and phosphate (pH 6.8) buffers, dissolution of all the tested products was not rapid (% drug dissolved within 30 min was less than 85 %). Dissolution of amoxicillin was complete within 15 min in pH 1.2 media, 90 min in pH 4.5 media and 45 min in pH 6.8 media, and the dissolution profiles of the tested products (Teva® and Kent®) were similar to the dissolution profile of the reference product (Amoxil®) ($f_2 \geq 50$; Table 6.3). Consequently, the products would not qualify for biowaiver status. These results are in agreement with dissolution studies recently conducted based on USP

methodologies and BCS-based biowaiver dissolution studies, which have showed high failure rates for amoxicillin products (28-30). In these studies, the discrepant dissolution profiles were thought to be caused by poor manufacturing techniques or variation in the API particle size, and thus with appropriate content uniformity assays in addition to *in vitro* drug dissolution testing, this risk should be easily identified (28-30). This could also be the case in this study, as the formulations selected do not contain any excipients known to affect the bioavailability of amoxicillin (Table 6.1), according to the available literature (18). Under setup 2 conditions, more than 85 % of the labelled amount of amoxicillin was dissolved in less than 15 min at pH 1.2, and under 30 min at pH 4.5 and 6.8 for all products tested. Complete dissolution was achieved within 20 min in pH 1.2 media, and 45 min in pH 4.5 and 6.8 media. Similarity comparison of the Teva® and Kent® products with the reference product showed that biowaiver status would be granted (pH 1.2: all products *rapidly* dissolved; pH 4.5: f_2 = 60.6 (Amoxil®-Kent®) and 62.8 (Amoxil®-Teva®); pH 6.8: f_2 = 73.1 (Amoxil®-Kent®) and 61.0 (Amoxil®-Teva®)). Since *in vitro* equivalence was shown between Amoxil® and the test products, the amoxicillin Teva® and Kent® capsules would be assumed as therapeutically equivalent to the reference product, under these testing conditions. With setup 3 conditions, the criterion for rapid dissolution was not met within the pH range tested. Dissolution was complete at pH 1.2 and 6.8 (within 15 and 75 min, respectively), but not at pH 4.5. Therefore, even though the products were shown to be similar ($f_2 \geq 50$; Table 6.3), they would not qualify for biowaiver status. The different results obtained with setups 1 and 3 in comparison to setup 2 testing conditions may be related to the dissolution setup. When using a dissolution volume of 250 mL in USP II dissolution (setup 2), the paddles are very close to the medium surface, which not only requires careful sampling as it may lead to result variability but also shows that the different hydrodynamics impact drug dissolution, ultimately affecting the outcome of the product qualification for a BCS-based biowaiver.

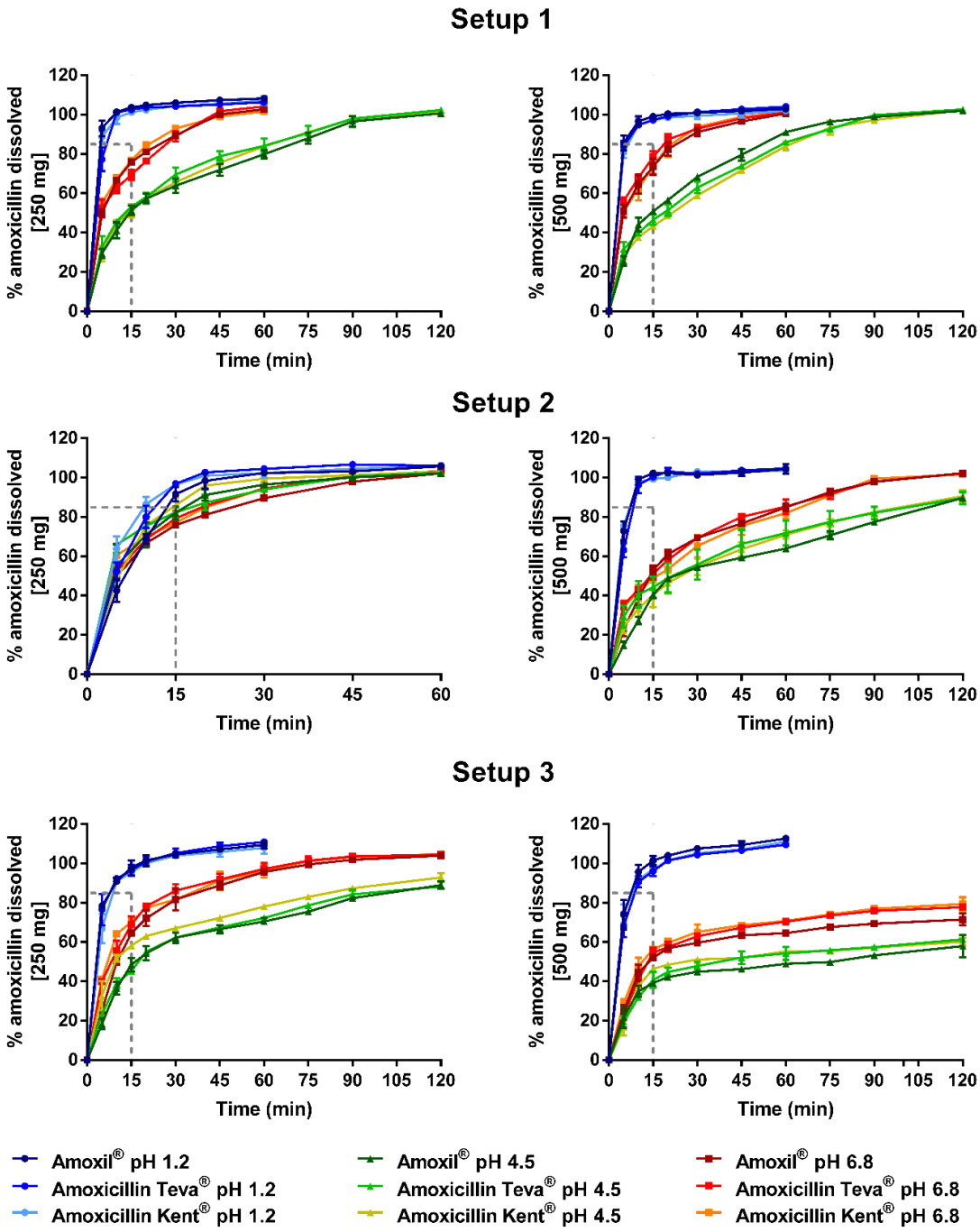


Figure 6.3. Mean % amoxicillin dissolved (± S.D.) from Amoxil®, amoxicillin Teva® and amoxicillin Kent® capsules 250 mg (left panels) and 500 mg (right panels), in SGF*sp* pH 1.2 (blue), acetate buffer pH 4.5 (green) and phosphate buffer pH 6.8 (red). Three setup scenarios were tested: (1) 900 mL, USP II apparatus; (2) 250 mL, USP II apparatus; (3) 50 mL, mini-paddle apparatus (from top to bottom). Dotted grey lines represent the limit for '*very rapid dissolution*' classification (> 85 % dissolved within 15 min).

Table 6.3. f_2 similarity factor values for the comparison between drug dissolution from the test and the reference formulation ($f_2 \geq 50$ noting similarity; red values: $f_2 <$ denoting non similarity between profiles). (-) % drug dissolved > 85% within 15 min.

	f_2 value	**Amoxicillin - 250 mg**			**Amoxicillin - 500 mg**		
		pH 1.2	***pH 4.5***	***pH 6.8***	***pH 1.2***	***pH 4.5***	***pH 6.8***
Setup 1	Amoxil® *vs* Kent®	-	68.35	68.49	-	53.91	66.18
	Amoxil® *vs* Teva®	-	78.17	74.03	-	56.55	85.12
Setup 2	Amoxil® *vs* Kent®	-	60.55	73.05	-	55.59	63.03
	Amoxil® *vs* Teva®	-	62.83	60.97	-	63.92	62.25
Setup 3	Amoxil® *vs* Kent®	-	78.99	54.16	-	69.23	66.96
	Amoxil® *vs* Teva®	-	51.17	51.09	-	63.28	62.40
		Prednisolone - 5 mg			**Prednisolone - 25 mg**		
		pH 1.2	***pH 4.5***	***pH 6.8***	***pH 1.2***	***pH 4.5***	***pH 6.8***
Setup 1	Pevanti® *vs* Actavis®	-	-	-	-	72.41	53.99
Setup 2	Pevanti® *vs* Actavis®	-	-	-	-	**47.47**	**37.99**
Setup 3	Pevanti® *vs* Actavis®	-	-	-	83.83	73.09	81.59
		Amlodipine - 5 mg			**Amlodipine - 10 mg**		
		pH 1.2	***pH 4.5***	***pH 6.8***	***pH 1.2***	***pH 4.5***	***pH 6.8***
Setup 1	Istin® *vs* Sandoz®	-	-	65.91	-	-	**48.35**
	Istin® *vs* Teva®	-	-	58.28	-	-	50.69
Setup 2	Istin® *vs* Sandoz®	-	-	-	-	-	**40.02**
	Istin® *vs* Teva®	-	-	-	-	-	64.26
Setup 3	Istin® *vs* Sandoz®	-	-	-	-	-	81.42
	Istin® *vs* Teva®	-	-	-	-	-	52.71

For the 500 mg capsules, the amoxicillin products would not qualify for a BCS-biowaiver under any of the setup conditions tested. Even though similarity was shown between the test and reference products ($f_2 \geq 50$; Table 6.3), the criterion for rapid dissolution was not met in any of the setups tested (setup 1 to 3; pH 1.2: all products *rapidly* dissolved; pH 4.5: % drug dissolved within 30 min was less than 85 %; pH 6.8: drug dissolved within 30 min was less than 85 % under setup 2 and 3 conditions). Under setup 1 conditions, complete dissolution was achieved in all

media pH (100 % drug dissolved reached within 15, 90 and 45 min at pH 1.2, 4.5 and 6.8, respectively). Under setup 2 conditions, complete dissolution was achieved in pH 1.2 and 6.8 media within 10 and 90 min, respectively, but not in pH 4.5 media. Under setup 3 conditions, complete dissolution was only achieved in pH 1.2 media, at pH 4.5 and 6.8 the maximum % dissolved within 2 h was 60 and 80 %, respectively. These results show a clear impact of the pH-drug solubility profile on drug dissolution behaviour. Amoxicillin is an amphoteric compound (18); in acidic pH it is protonated, in a pH typical of the upper small intestine it exists primarily as a zwitterion, and in the distal small intestine (pH 6.5) it will exist both as zwitterion and as deprotonated acid. It has been shown to exhibit a pH-dependent, *U*-shaped solubility curve (drug solubility in buffers of pH 1.2, 4.5, and 6.8 was 7.7, 3.6 and 5.4 mg/mL, respectively) (18). Accordingly, drug dissolution rate was higher at pH 1.2, which can be correlated with the higher drug solubility in acidic conditions due to an increase in the ionisation % of the drug. For the 250 mg products (setup 3) and 500 mg products (all setups), sink conditions were not achieved during the dissolution studies (*i.e.* having a volume of medium at least three times above the volume required to form a saturated drug solution (31)). Sink conditions are critical to ensure that reproducible dissolution occurs; however, although these conditions are desirable, accordingly to BCS-based biowaiver regulations, they are not mandatory and the important is to have a discriminative method (8-10, 31).

Overall, the 250 mg amoxicillin products tested would fail to meet the *in vitro* dissolution criterion associated with the BCS-based biowaiver requirements in setups 1 and 3 conditions and would pass in setup 2 conditions. As previously mentioned, the difference in outcomes between setup 2 conditions and the other setups is likely related to the impact of hydrodynamics. For the 500 mg amoxicillin capsules, the tested products would fail to meet BCS-based biowaiver requirements in all the setup scenarios tested.

Amoxicillin is a broad spectrum, beta-lactam antibiotic, mainly used in an ambulatory setting for infections of mild-to-moderate severity (18, 32). Since it has a wide therapeutic range (33), the possibility of life-threatening toxic reactions with supra-therapeutic doses of amoxicillin is very low. On the other hand, the risk associated with subtherapeutic blood levels is unknown; a false-positive biowaiver decision, particularly if the products are severely below the accepted level of

bioequivalence, could possibly lead to prolongation of illness, and even to the development of resistance if the drug content significantly differs from the labelled amount (34). In this study, since in setup 1 conditions the products do not exhibit rapid dissolution in pH 4.5, then it would not be possible to get a biowaiver for an adult formulation. Moreover, since the paediatric population undergoes developmental changes (*e.g.* gastric pH and emptying, intestinal transit time, membrane permeability, body water, distribution and metabolism), which may lead to a significant alteration of the plasma concentration profile and of key bioequivalence parameters (*e.g.* C_{max} and AUC), bioinequivalence risks might be increased in this population (12, 35). Consequently, a BCS-based biowaiver status of these products could not be applied for administration in paediatrics.

3.2 Prednisolone

Dissolution profiles of prednisolone from the products tested (reference: Pevanti®; test: Actavis®) are presented in Figure 6.4 and f_2 similarity factor results are shown in Table 6.3. Results of dissolution studies of the 5 mg prednisolone tablets revealed that more than 85 % of the labelled amount of prednisolone was dissolved in less than 15 min, under all the setup scenarios tested. Under setup 1 and 2 conditions, complete dissolution was achieved in pH 1.2 and 6.8 media within 15 min and in pH 4.5 media within 20 min. Under setup 3 conditions, complete dissolution was achieved in all pH within 30 min. Due to having met *very rapidly* dissolution criterion, *in vitro* equivalence was shown between prednisolone Actavis® and Pevanti® tablets, in all the setup testing conditions performed. The test product can be assumed as therapeutically equivalent to the reference, with no need for *in vivo* bioequivalence studies.

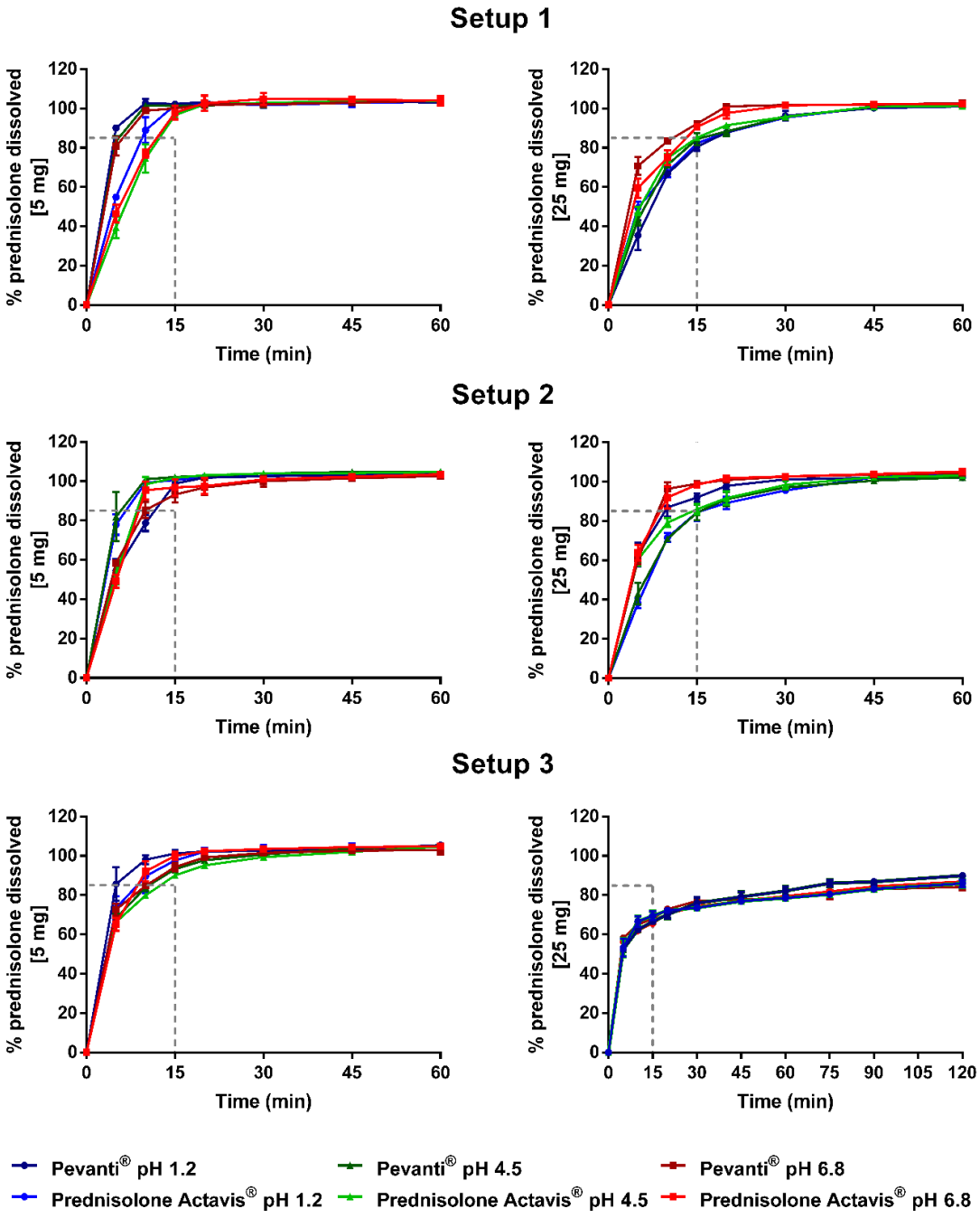


Figure 6.4. Mean % prednisolone dissolved (± S.D.) from Pevanti® and prednisolone Actavis® tablets 5 mg (left panels) and 25mg (right panels), in SGF*sp* pH 1.2 (blue), acetate buffer pH 4.5 (green) and phosphate buffer pH 6.8 (red). Three setup scenarios were tested: (1) 900 mL, USP II apparatus; (2) 250 mL, USP II apparatus; (3) 50 mL, mini-paddle apparatus (from top to bottom). Dotted grey lines represent the limit for '*very rapid dissolution*' classification (> 85 % dissolved within 15 min).

For the 25 mg tablets, under setup 1 conditions, complete dissolution was achieved in pH 1.2 media within 20 min and in pH 4.5 and 6.8 media within 45 min. Comparison of the dissolution studies of the test (Actavis®) and the reference

(Pevanti®) products showed that following BCS-based dissolution testing conditions, biowaiver status would be granted (*rapidly* dissolved products; $f_2 \geq 50$; Table 6.3). Under setups 2 and 3 dissolution conditions, the products would not qualify for biowaiver status. Under setup 2 dissolution conditions, although more than 85 % of the labelled drug amount in the dosage form was dissolved in less than 30 min, f_2 analysis revealed that the test and reference products were not similar (pH 4.5 and 6.8: f_2 (Actavis®-Pevanti®) = 47.5 and 38.0, respectively). Under these conditions, complete dissolution was achieved within 20 min in pH 1.2 media and within 45 min in pH 4.5 and 6.8 media. When testing under setup 3 dissolution conditions (mini-paddle apparatus, 125 rpm, 50 mL), the test product would not qualify for BCS-based biowaiver status since rapid dissolution criterion (> 85 % dissolved in less than 30 min) was not met, even though f_2 analysis revealed similarity between test and reference products ($f_2 > 50$; Table 6.3). Sink conditions in dissolution testing of both products were not achieved with this dose (25 mg) in 50 mL, as revealed by the lower dissolution (maximum % drug dissolved at 2 h was 89.0 and 85.5 %, for Pevanti® and Actavis®, respectively).

Overall, the 5 mg prednisolone products tested would meet the *in vitro* dissolution criterion associated with the BCS-based biowaiver requirements, in all the setup conditions tested. For the 25 mg tablets, the products would meet BCS-based biowaiver requirements in setup 1 conditions, but not under setup 2 and 3 conditions tested.

According to drug solubility and permeability studies, prednisolone can be classified as a BCS Class I drug (19). When calculating the D_0 for the 25 mg tablets, prednisolone was shown to change solubility class to low solubility in younger age groups (Table 6.2). This is reflected in the results obtained when testing the 25 mg formulations, under setup 2 and 3 conditions. In this context, formulation bridging into paediatrics could result in a false biowaiver decision (*i.e.* wrongly declaring the test formulation bioequivalent to the reference formulation in the paediatric population). This could affect the *in vivo* drug behaviour, resulting in changes in the AUC and/or C_{max} of the drug. If resulting in a lower AUC, the products might be clinically less effective in paediatric patients and/or potentially lead to serious clinical consequences when acute treatment is required for severe, life-threatening diseases. In this case, as prednisolone is a prescription-only drug, therapy should be

periodically reviewed a dose adjustment/ substitution would be required. If the drug became supra-bioavailable (*i.e.* resulted in a higher AUC than intended), the risk of toxicity and/or side effects would increase (19, 36). Lastly, if bioinequivalence was caused by a difference in C_{max}, clinical implications could be expected since prednisolone IR tablets are usually used in chronic therapeutic regimes (37).

3.3 Amlodipine

Dissolution of amlodipine from the products tested (reference: Istin®; test: Sandoz® and Teva®) and f_2 similarity factor results are presented in Figure 6.5 and Table 6.3, respectively. For the 5 mg tablets, under setup 1 testing conditions, more than 85 % of amlodipine was dissolved within 15 min, in the pH 1.2 and pH 4.5 media. At pH 6.8, although f_2 analysis revealed similarity between the dissolution profiles of the tested products in relation to the reference, the criterion for rapid dissolution was not met (*i.e.* 85% of drug dissolution within 30 min). Therefore, the products would not qualify for biowaiver status. Complete dissolution was achieved in pH 1.2 and 4.5 media within 10 min and in pH 6.8 media within 60 min. The lower dissolution rate observed at pH 6.8 could be explained by drug characteristics; since amlodipine is a weak base (pKa 8.7 (38)), it is affected by changes in pH and exhibits pH-dependent solubility (20, 38). Under setups 2 and 3 conditions, more than 85 % of the labelled amount of amlodipine was dissolved in less than 15 min. Having met the *very rapidly* dissolution criterion, *in vitro* equivalence was shown between the test products and the reference, and the products would qualify for BCS-biowaiver status.

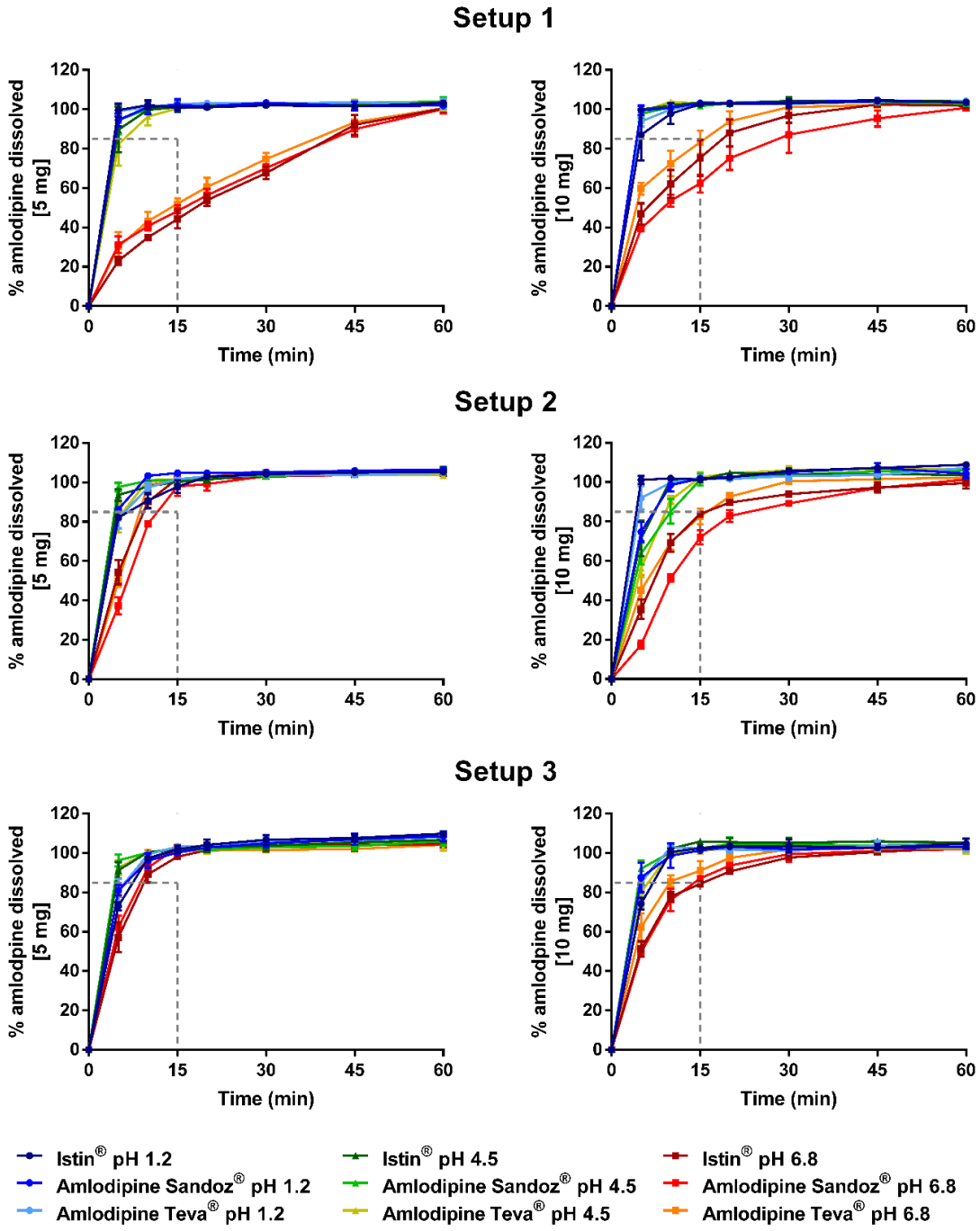


Figure 6.5. Mean % amlodipine dissolved (± S.D.) from Istin®, amlodipine Sandoz® and amlodipine Teva® tablets 5 mg (left panels) and 10 mg (right panels), in SGF*sp* pH 1.2 (blue), acetate buffer pH 4.5 (green) and phosphate buffer pH 6.8 (red) under three testing scenarios. Three setup scenarios were tested: (1) 900 mL, USP II apparatus; (2) 250 mL, USP II apparatus; (3) 50 mL, mini-paddle apparatus (from top to bottom). Dotted grey lines represent the limit for '*very rapid dissolution*' classification (≥ 85 % dissolved within 15 min).

For the 10 mg tablets, under setup 1 (BCS-based dissolution testing) and setup 2 conditions, % drug dissolved was higher than 85 % under 15 min at pH 1.2 and 4.5,

and under 30 min at pH 6.8, for all products tested. Under both setup conditions, complete dissolution was achieved within 15 min in media of pH 1.2 and 4.5, and within 45 (setup 1) or 60 (setup 2) min at pH 6.8. Similarity comparison of the Teva® and Istin® (reference) tablets showed that biowaiver status would be granted for the test product (pH 1.2 and 4.5: *rapidly* dissolved products; pH 6.8: f_2 (Istin®-Teva®) = 50.7 and 64.3 for setups 1 and 2, respectively). On the contrary, comparison of Sandoz® and reference (Istin®) tablets showed that biowaiver status would not be granted for the test product (pH 1.2 and 4.5: *rapidly* dissolved products; pH 6.8: f_2 (Istin®-Sandoz®) = 48.4 and 40.0 for setups 1 and 2, respectively). In the case of the formulations tested (10 mg tablets), dissolution of amlodipine could be affected by the excipients used and/or manufacturing methods. Since the excipients included in the selected formulations would not be expected to affect drug behaviour (Table 6.1), it is more likely that the differences observed in drug dissolution from the tested formulations are due to manufacturing methods causing variability in the results. Under setup 3 conditions (mini-paddle, 50 mL, 125 rpm), complete dissolution was achieved in pH 1.2 and 4.5 media within 10 min and in pH 6.8 media within 45 min. % drug dissolved was higher than 85 % under 15 min at pH 1.2 and 4.5, and under 30 min at pH 6.8 for all products tested, and f_2 analysis revealed similarity between all products (pH 1.2 and 4.5: *rapidly* dissolved products; pH 6.8: f_2 (Istin®-Sandoz®) = 81.4, f_2 (Istin®-Teva® = 52.7)). Therefore, biowaiver status would be granted for all products.

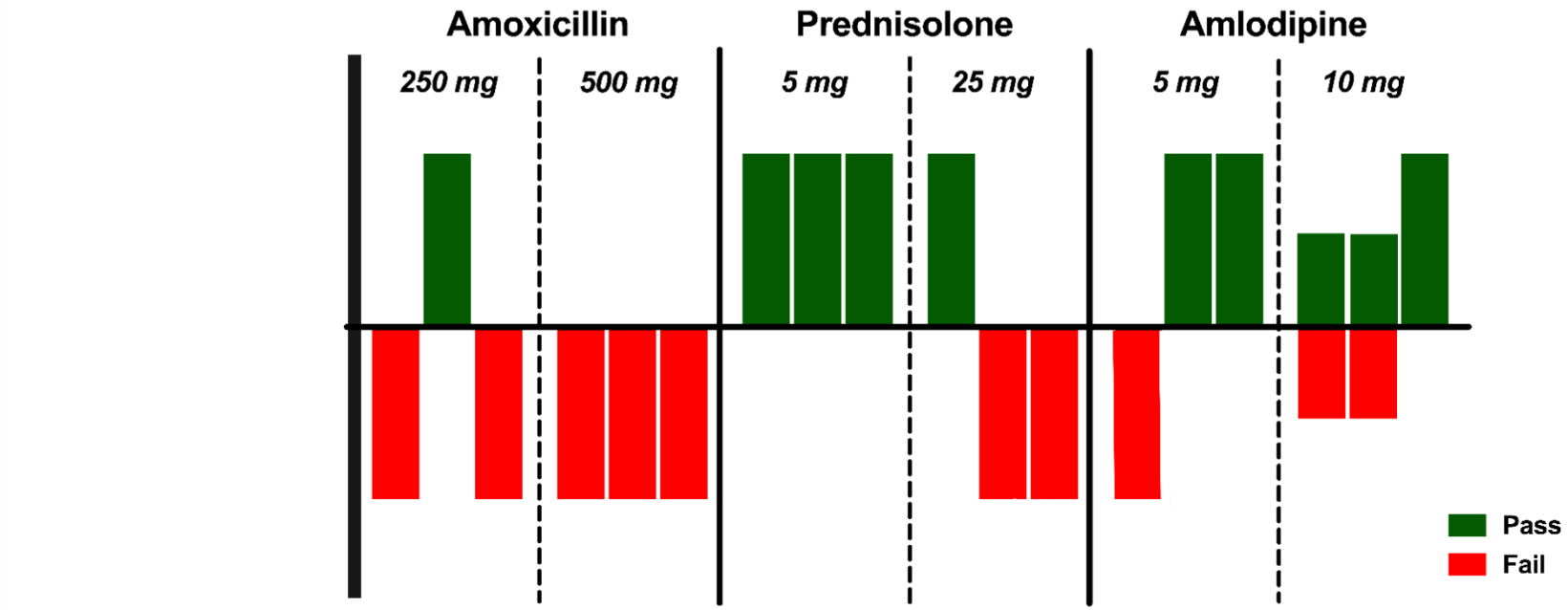
Overall, results revealed that the 5mg amlodipine tablets tested would fail to meet the *in vitro* dissolution criterion associated with the BCS-based biowaiver requirements in setup 1 conditions and would pass in setup 2 and 3 conditions. Regarding the 10 mg amlodipine tablets, the Istin® and Teva® products would qualify for a BCS-based biowaiver status under all setup scenarios tested, while the Sandoz® products would not qualify for a biowaiver status in setup 1 and 2 conditions but would qualify in setup 3 conditions.

Regarding evaluating patient risks associated with bioinequivalence, a false-positive biowaiver decision for amlodipine IR dosage forms could result in subtherapeutic plasma concentrations (which may lead to a therapeutic failure) or to concentrations above the recommended upper therapeutic concentrations (which may result in adverse drug reactions). Amlodipine is indicated for hypertension (38-40). In

general, drug dose is individualized depending on the severity of disease, tolerance and responsiveness of the patient to the drug (40). In these situations, it is necessary to ensure BE of the product, so that the therapeutic outcome from treatment with test products could be well predicted during the management of pharmacological indications. As far as supra-therapeutic drug levels, mild to moderate side effects have been reported (40). Patient risks associated with the sub-therapeutic levels pose more serious consequences because of therapeutic insufficiency; these can be exacerbated in very young age groups as a recent study has shown that amlodipine dosing has a significant inverse relationship with patient age, with the youngest children requiring the highest doses of amlodipine (39).

3.4 Risk assessment of extending BCS-based biowaiver criteria into paediatrics

A summary of the results obtained in this study and of whether the biowaiver status (as currently defined) would be granted in each situation is presented in Figure 6.6. Results revealed that only the 5 mg prednisolone and the 10 mg amlodipine tablets (Istin® and Teva® but not Sandoz®) would qualify for a biowaiver status, under all setup scenarios tested. In view of these results, it seems clear that extrapolation of the BCS-based biowaiver criteria into paediatrics is not straightforward and cannot be based on direct assumptions (*i.e.* simple scaling down).



BCS Biowaiver Criteria	Setup																	
	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
>85% dissolved in 15 min	-	-	-	-	-	-	+	+	+	-	-	-	-	+	+	-	-	N/A
>85% dissolved in 30 min	-	+	-	-	-	-	N/A	N/A	N/A	+	+	-	-	N/A	N/A	+/-	+	+
f_2	+	+	+	+	+	+	N/A	N/A	N/A	+	-	+	+	N/A	N/A	+/-	+/-	+

Figure 6.6. Risk assessment of extending the biowaiver for IR formulations of 3 model compounds from the adult to the paediatric population. (N/A: not applicable). Green and red colours represent if the products would pass or fail, respectively, the rapid dissolution criteria. [(+): follows the criterion; (-): fails the criterion]

When analysing the risk of extending BCS-based biowaiver testing criteria into products for the paediatric population, it is important to consider the factors that would affect BCS-based biowaiver decisions and the relevance of the criteria within the paediatric population. BCS-based biowaiver decisions are allowed for highly soluble drugs, which are expected to exhibit fast dissolution rates. Currently, drugs are classified as highly soluble if the highest dose strength is soluble in at least 250 mL of aqueous liquid at a relevant physiological pH range of 1.2 – 6.8, however these aspects concern adult physiology. Age-related changes in anatomy and physiology will impact the classification of drug solubility and permeability properties within the different paediatric subpopulations. Several issues arise regarding drug solubility classification amongst the paediatric population, including the definition of the highest single dose, the initial gastric volume, and the luminal solubility of the drug. Moreover, with respect to drug permeability classification, drugs are classified as highly permeable when the extent of oral absorption (*i.e.* fraction of dose absorbed) is greater than 85 % of the administered dose. However, using adult permeability data for paediatric subjects is controversial and information regarding permeability in younger paediatric subgroups is still lacking, which has hindered the establishment of meaningful permeability criteria for this population. Thus, a drug that exhibits a high dose/solubility ratio in adults (*i.e.* highly soluble drug) might not show the same ratio in paediatric patients, and unfavourably shift into poorly soluble classification. In this study, except for the case of prednisolone in a dose of 5 mg, the chosen model compounds selected would change from high drug solubility classification in adults to low drug solubility class in paediatric age groups (D_0 > 1; Table 6.2). These drugs would not be eligible for BCS-based biowaiver status, as the solubility criterion was not satisfied. In this context, a p-BCS approach could provide a simplistic tool to help understand possible age-related physiological and/or anatomical changes in oral drug performance, and identify risks associated with a change in BCS class of a compound and eligibility for BCS-based biowaivers for paediatric products.

Regarding testing methodology, dissolution testing with USP I/II apparatus is commonly used to define the classification of a drug when rapid dissolution across a pH range is required (which is the case for BCS-based biowaivers). The basis of this approach is that the dosage form is agitated at a fixed rate within a fixed media

volume, representative of the GI environment. Some limitations associated with this apparatus have been reported, including the impossibility of using small testing volumes (26, 41). This is of importance as the fluid volumes available in the GI tract of younger age groups are smaller than adults (35). In the present study, an adaptation of standard USP II apparatus to a mini-paddle apparatus was tested as an appropriate method to address the need for small volume testing. The mini-paddle apparatus is already commonly used when screening for critical quality attributes of rapid dissolving tablets, in cases where it is difficult to detect differences using standard working conditions (41). Regarding agitation rate criterion, rates of 50 and 100 rpm have been defined for paddle and basket apparatus, respectively (1, 8, 14). A direct extrapolation was made from the agitation rates set for the USP II apparatus (50 or 75 rpm) to the mini-paddle following a speed factor, which allowed the maintenance of discriminatory conditions.

The dissolution media volume was considered in this study and its effect on drug dissolution was evaluated by comparison of different setup conditions. Since there is currently no guidance on appropriate volumes to use within paediatric dissolution testing, a direct extrapolation from the adult value of 250 mL utilised in USP II dissolution was conducted for the mini-paddle apparatus (50 mL; setup 3). As previously mentioned, an important factor in BCS-style bridging is that dissolution rate of paediatric medicines needs to be rapid to ensure adequate exposure in this population and guarantee that GI transit dictates drug absorption rather that drug dissolution. In this context, BCS-based biowaiver would be granted for the 5 mg prednisolone and 10 mg amlodipine tablets (Istin® and Teva® but not Sandoz®) but all the amoxicillin products (250 and 500 mg), the lowest dose amlodipine products and the highest dose products of prednisolone would fail to be classified as *rapidly* dissolved. In the case of the amlodipine 5 mg tablets, the products would fail the criterion of rapid dissolution under setup 1 conditions (current requirements for BCS-based biowaivers) due to slow dissolution in pH 6.8 but would pass when the volume was scaled down (setups 2 and 3). In the case of the prednisolone 25 mg tablets, the products would meet the criterion of rapid dissolution under setup 1 conditions (current requirements for BCS-based biowaivers), but would fail when the volume was scaled down, likely due to the solubility of the drug.

The time limits set to define rapid dissolution criteria might also affect the biowaiver status, as subsequent analysis of the dissolution profiles differs accordingly. For example, in the present study it was shown that when the products did not meet the criteria for *very rapidly* or *rapidly* dissolving products, it was because both the test and reference products did not exhibit fast dissolution and not due to dissimilarity between profiles (except for the case of the Sandoz® amlodipine 10 mg tablets). This could indicate that the time frame for rapid drug dissolution should be further evaluated, and potentially refined when considering the paediatric population. A minimum of 50 % of drug release within 15 min has been recently suggested to support a biowaiver decision for paediatric formulations (21). With this criterion, the formulations studied in mini-paddle setup would be considered as *rapidly* dissolved, except for the case of amoxicillin 500 mg capsules for which drug dissolution was shown to be limited by drug solubility. Nevertheless, the scientific basis for such alterations regarding the most appropriate time frames for evaluating dissolution rates, would need to be further evaluated.

Overall, the risk of using the BCS adult classification in paediatric drug development lies in shifts in BCS classification of drugs due to growth and maturation of paediatric subpopulations. Results from this study reveal the need for the development and establishment of a p-BCS, as a simplistic tool to help understand possible changes in oral drug performance in the paediatric population. The development and establishment of a p-BCS could meaningfully impact the paediatric biopharmaceutical field and guide the production of age-appropriate medicines and facilitate formulation bridging. While such a tool remains to be developed, extrapolation of the adult BCS classification should be performed with care.

4. Conclusions

The use of BCS-based biowaivers for paediatric products needs to be undertaken with caution due to differences in the drug D_0 between adults and paediatrics.

In this study, the risk of directly extrapolating BCS-based criteria into paediatrics was assessed. A dissolution setup potentially representative of the paediatric population in terms of the lower volumes required was tested (setup 3), with the

criteria limits used in BCS-based biowaiver guidance being applied for product evaluation/risk assessment. Results revealed that only the 5 mg prednisolone and the 10 mg amlodipine tablets (Istin® and Teva® but not Sandoz®) would qualify for a biowaiver status, under all setup scenarios tested. Thus, it was shown that a simple scaling down of the dissolution testing volume stipulated on BCS-based biowaiver dissolution criteria may not be adequate for paediatric products. Knowledge of the solubility classification of a drug across different age groups would assist on assessing the development of a biowaiver as BE testing surrogate in the different age groups. Therefore, a consensus on a p-BCS needs to be reached and should address the heterogeneity of the paediatric population.

Overall, the establishment of a p-BCS would contribute to formulation bridging (*e.g.* surrogate the need for future clinical BE testing) and risk assessment decisions, thus promoting paediatric drug development. This would result in a smaller discrepancy between technologies available for the different age groups and provide better support for the development and testing of age-appropriate medicines, ultimately leading to a minimisation of clinical trials and regulatory burden.

References

1. Batchelor HK, Kendall R, Desset-Brethes S, Alex R, Ernest TB, Initiative EPF. Application of in vitro biopharmaceutical methods in development of immediate release oral dosage forms intended for paediatric patients. Eur J Pharm Biopharm. 2013;85(3):833-42.

2. Daousani C, Karalis VD. Paediatric medicines: regulatory and scientific issues. Drug Res. 2017;67(07):377-84.

3. Elder DP, Holm R, Kuentz M. Medicines for pediatric patients—biopharmaceutical, developmental, and regulatory considerations. J Pharm Sci. 2017;106(4):950-60.

4. Batchelor H. Paediatric biopharmaceutics classification system: current status and future decisions. Int J Pharm. 2014;469(2):251-3.

5. Giacoia GP, Taylor-Zapata P, Zajicek A. Eunice Kennedy Shriver National Institute of Child Health and Human Development pediatrics formulation initiative: proceedings from the second workshop on pediatric formulations. Clin Ther. 2012;34(11):S1-S10.

6. Ricci BM. Bridging studies in support of oral pediatric formulation development. Int J Pharm. 2013;457(1):323-6.

7. Amidon GL, Lennernäs H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm Res. 1995;12(3):413-20.

8. Food and Drug Administration. Guidance for industry: waiver of in vivo bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a biopharmaceutics classification system. 2017. https://www.fda.gov/downloads/Drugs/Guidances/ucm070246.pdf. Assessed 5 January 2019.

9. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP): Guideline on the investigation of bioequivalence. 2010. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-bioequivalence-rev1_en.pdf. Assessed 5 January 2019.

10. World Health Organization. Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms. 2006. https://www.who.int/medicines/services/expertcommittees/pharmprep/QAS04_109Rev1_Waive_invivo_bioequiv.pdf. Assessed 5 January 2019.

11. Batchelor H, Ernest T, Flanagan T, Klein S, Turner R, Fotaki N, et al. Towards the development of a paediatric biopharmaceutics classification system: results of a survey of experts. Int J Pharm. 2016;511(2):1151-7.

12. Guimarães M, Statelova M, Holm R, Reppas C, Symilllides M, Vertzoni M, et al. Biopharmaceutical considerations in paediatrics with a view to the evaluation of orally administered drug products–a PEARRL review. J Pharm Pharmacol. 2019;71(4):603-42.

13. Selen A, Cruañes MT, Müllertz A, Dickinson PA, Cook JA, Polli JE, et al. Meeting report: applied biopharmaceutics and quality by design for dissolution/release specification setting: product quality for patient benefit. Springer; 2010.

14. Purohit VS. Biopharmaceutic planning in pediatric drug development. AAPS J. 2012;14(3):519-22.

15. Gandhi SV, Rodriguez W, Khan M, Polli JE. Considerations for a Pediatric Biopharmaceutics Classification System (BCS): application to five drugs. AAPS PharmSciTech. 2014;15(3):601-11.

16. Shawahna R. Pediatric biopharmaceutical classification system: using age-appropriate initial gastric volume. AAPS J. 2016;18(3):728-36.

17. World Health Organization. The Selection and Use of Essential Medicines: Report of the WHO Expert Committee, 2017 (including the 20th WHO Model List of Essential Medicines and the 6th WHO Model List of Essential Medicines for Children). 2017. https://apps.who.int/iris/bitstream/handle/10665/259481/9789241210157-eng.pdf?sequence=1&isAllowed=y. Assessed 8 January 2019.

18. Thambavita D, Galappatthy P, Mannapperuma U, Jayakody L, Cristofoletti R, Abrahamsson B, et al. Biowaiver monograph for immediate-release solid oral dosage forms: amoxicillin trihydrate. J Pharm Sci. 2017;106(10):2930-45.

19. Vogt M, Derendorf H, Krämer J, Junginger H, Midha K, Shah V, et al. Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms: Prednisolone. J Pharm Sci. 2007;96(1):27-37.

20. Shohin I, Ramenskaya G, Vasilenko G, Malashenko E. In vitro dissolution kinetics of amlodipine tablets marketed in Russia under biowaiver conditions. Dissolut Technol. 2010;17(3):20-3.

21. Abdel-Rahman SM, Amidon GL, Kaul A, Lukacova V, Vinks AA, Knipp GT, et al. Summary of the national institute of child health and human development–best pharmaceuticals for children act pediatric formulation initiatives workshop–pediatric biopharmaceutics classification system working group. Clin Ther. 2012;34(11):S11-S24.

22. Wishart DS, Knox C, Guo AC, Cheng D, Shrivastava S, Tzur D, et al. DrugBank: a knowledgebase for drugs, drug actions and drug targets. Nucleic Acids Res. 2007;36(suppl_1):D901-D6.

23. Crawford M, Lerman J, Christensen S, Farrow-Gillespie A. Effects of duration of fasting on gastric fluid pH and volume in healthy children. Anesth Analg. 1990;71(4):400-3.

24. Goetze O, Treier R, Fox M, Steingoetter A, Fried M, Boesiger P, et al. The effect of gastric secretion on gastric physiology and emptying in the fasted and fed state assessed by magnetic resonance imaging. Neurogastroenterol Motil. 2009;21(7):725-e42.

25. USP 30 - NF 25. United States Pharmacopeia convention. Rockville, USA; 2007.

26. Scheubel E, Lindenberg M, Beyssac E, Cardot J-M. Small volume dissolution testing as a powerful method during pharmaceutical development. Pharmaceutics. 2010;2(4):351-63.

27. Shah VP, Tsong Y, Sathe P, Liu J-P. In vitro dissolution profile comparison—statistics and analysis of the similarity factor, f2. Pharm res. 1998;15(6):889-96.

28. Löbenberg R, Chacra NB, Stippler ES, Shah VP, DeStefano AJ, Hauck WW, et al. Toward global standards for comparator pharmaceutical products: case studies of amoxicillin, metronidazole, and zidovudine in the Americas. AAPS J. 2012;14(3):462-72.

29. Reddy NH, Patnala S, Löbenberg R, Kanfer I. In vitro dissolution of generic immediate-release solid oral dosage forms containing BCS class I drugs: comparative assessment of metronidazole, zidovudine, and amoxicillin versus relevant comparator pharmaceutical products in South Africa and India. AAPS PharmSciTech. 2014;15(5):1076-86.

30. Stuart AV, Zuo J, Löbenberg R. Investigating the Dissolution Profiles of Amoxicillin, Metronidazole, and Zidovudine Formulations used in Trinidad and Tobago, West Indies. AAPS PharmSciTech. 2014;15(5):1060-9.

31. Gibaldi M, Feldman S. Establishment of sink conditions in dissolution rate determinations. Theoretical considerations and application to nondisintegrating dosage forms. J Pharm Sci. 1967;56(10):1238-42.

32. Eyer CL. Goodman & Gilman's: The Pharmacological Basis of Therapeutics. Am J Pharm Educ. 2002;66(1):95.

33. Doogue MP, Polasek TM. Drug dosing in renal disease. Clin Biochem Rev. 2011;32(2):69.

34. Gustafsson I, Löwdin E, Odenholt I, Cars O. Pharmacokinetic and pharmacodynamic parameters for antimicrobial effects of cefotaxime and amoxicillin in an in vitro kinetic model. Antimicrob Agents Chemother. 2001;45(9):2436-40.

35. Batchelor HK, Fotaki N, Klein S. Paediatric oral biopharmaceutics: key considerations and current challenges. Adv Drug Deliv Rev. 2014;73:102-26.

36. Robinson J, McKenzie C, MacLeod D. Paediatric dosing errors with oral prednisolone mixture. Aust Prescr. 2016;39(5):176.

37. BNF for Children (BNFC) 2016-2017: Royal Pharmaceutical Society of Great Britain, British Medical Association, Pharmaceutical Press; 2017.

38. Van Zwieten P. Amlodipine: an overview of its pharmacodynamic and pharmacokinetic properties. Clin Cardiol. 1994;17(9 Suppl 3):III3.

39. Flynn JT, Smoyer WE, Bunchman TE. Treatment of hypertensive children with amlodipine. Am J Hypertens. 2000;13(10):1061-6.

40. Murdoch D, Heel RC. Amlodipine - A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in cardiovascular disease Drugs. 1991;41(3):478-505.

41. Crist GB. 2009 Trends in Small-Volume Dissolution Apparatus for Low-Dose Compounds. Dissolut Technol. 2009;16(1):19-22.

Conclusions and future directions

Conclusions

Development of oral medicines for young patients is more challenging than for adults. Despite the increased effort put into improving the safety and effectiveness of paediatric medicines, formulation development is hindered by ethical considerations and technical constraints including physiological and anatomical changes. The tools currently used to undertake biopharmaceutical risk assessment of paediatric formulations are based on adult tests, addressing adult physiology and anatomy. Consequently, paediatric medicines are not always age-appropriate, leading to problems with dosing, acceptability and adherence.

In this project, research was conducted towards the development of *in vitro* predictive tools, to aid understanding of formulation performance and facilitate bridging in paediatrics. An emphasis was placed on co-administration of medicines with food and drinks (vehicles), and on a potential extension of Biopharmaceutical Classification System (BCS)-based biowaiver criteria into paediatric products.

Mixing oral dosage forms with food and drinks was revealed to be a common practice to facilitate paediatric medicine administration in order to improve palatability and enhance patient compliance. However, studies often fail to assess its impact on drug bioavailability, safety and efficacy. To reduce the need for manipulation and co-administration of medicines with vehicles, continuous efforts should be made towards developing age-appropriate medicines, whilst providing dosing flexibility and acceptable taste. Nevertheless, since this remains the most practiced strategy for paediatric oral administration, more elaborate and explicit information regarding vehicle suitability is warranted. In this context, the use of *in vitro* biopharmaceutical techniques to guide vehicle selection and assessment and predict *in vivo* performance in the paediatric population, could help understand the possible clinical outcomes associated with this practice, whilst allowing the availability of information for appropriate vehicle decisions.

First, a statistical model was developed which provided an understanding on which vehicle type is recommended for use with drugs/formulations, with basis on their biopharmaceutical properties.

Commonly recommended vehicles for medicine co-administration were then selected, and their physicochemical properties were studied, with differences observed not only among vehicle type, but also within vehicles of the same subtype. Solubility studies of two model compounds in commonly used vehicles was shown to be significantly affected by the physicochemical properties (pH, osmolality, buffer capacity, surface tension and viscosity) and macronutrient composition (percentage of fat, sugars and protein) of the vehicles.

Age-appropriate *in vitro* dissolution tests were to predict the impact of different administration practices of medicine co-administration with vehicles on drug behaviour. An *in vitro* dissolution testing setup under infant simulating conditions was developed, which could be used to evaluate drug dissolution, whilst addressing typical dosing conditions (*e.g.* co-administration with vehicles) and allowing the investigation of factors that could affect drug dissolution. Drug dissolution was shown to be significantly affected by medicine co-administration with vehicles, in comparison to the scenario of direct administration of formulation, and the time between preparation and testing of the drug-vehicle mixture. Prior knowledge of the properties of the vehicles was shown to be useful towards predicting their possible impact on drug behaviour. To predict *in vivo* formulation performance, paediatric biorelevant media was used in combination with the *in vitro* dissolution setup developed. The biorelevant *in vitro* dissolution test predicted the *in vivo* drug product performance in infant subgroups. Additionally, it was revealed that the practice of medicine co-administration with food and drinks might trigger fed state conditions *in vivo*. Ultimately, the potential of physiologically relevant dissolution studies with mini-paddle to mimic paediatric administration practices and predict drug performance was highlighted.

The use of BCS-based biowaivers in paediatrics was also investigated. A simple extension of current biowaiver criteria into the paediatric population was shown not to be feasible. Moreover, a discussion of factors that hinder the establishment of a paediatric-BCS in paediatrics identified knowledge gaps regarding the paediatric gastrointestinal (GI) tract, and technical and ethical constraints concerning clinical testing.

Overall, work was conducted towards identifying the areas where further information is needed to support knowledge around the paediatric biopharmaceutical field. It was demonstrated that the biopharmaceutical basis for the recommendation of co-administration of paediatric medicines with vehicles should be considered during administration practices and formulation testing, mainly due to the possible negative therapeutic outcomes. The need for unified mandatory guidelines on paediatric administration practices, including appropriate training of parents, carers and healthcare professionals and assessment methodologies, was emphasised and should be regulatory priority. Ultimately, it was shown that *in vitro* biopharmaceutical tools for investigation of drug product performance in paediatrics need further development, refinement and validation, which is still hindered by knowledge gaps and ethical and technical constraints. In this context, a combination of *in vitro* and *in silico* methods would be a stronger approach to ensure the prediction of paediatric drug product performance, having the potential to largely overcome the need to conduct *in vivo* research in this population.

We developed *in vitro* age-appropriate predictive tools to aid understanding of formulation performance in paediatrics. Our emphasis was on the impact of medicine co-administration with food/drinks and age-related factors on *in vitro* drug behaviour. We showed that knowledge of the composition and physiochemistry of food/drinks in combination with drug/formulation properties can appropriately guide their selection for medicine co-administration. *In vitro* testing can be used to predict the impact of different medicine co-administration practices on drug behaviour. Ultimately, these tools could be used to predict *in vivo* clinical outcomes.

Future directions

In this thesis, age-appropriate biopharmaceutical tools were defined in order to predict the impact of administration practices on drug product behaviour.

Commonly reported techniques of medicine co-administration with vehicles revealed the need for a unified mandatory regulation on administration practices, vehicle selection and assessment. This involves better training of healthcare professionals, and consequently patients, parents and carers, on the possible clinical outcomes of

this practice, supported by globally available platforms and unified databases. Initiatives such as the pan-European formulary are crucial, however further work should be conducted towards including information on this practice in these emerging platforms to better support paediatric pharmacotherapy.

In this project, a statistical model was developed which provided an understanding on which vehicle is recommended for use with drugs/formulations, with basis on their biopharmaceutical properties. This is a first approach towards generating awareness and discussion concerning co-administration practices of paediatric medicines, within the clinical and scientific communities. In the future, it would be useful to include information from other formularies not included to further refine and validate the model constructed.

Future experiments with different drugs and formulations (namely, of different BCS class, solubility, pKa, logP) would be valuable towards revealing the extent of the vehicle-impact on formulation performance. When combined with the physicochemical properties and composition of the vehicles, these could consequently be used to develop and establish a regulatory framework to guide administration practices, vehicle selection and assessment, and predict potential food effects. In addition, vehicles from the same subtype and different countries should be evaluated to expand the database created in Chapter 3. Ultimately, this would provide a useful tool for guidance both during paediatric formulation development and in clinical settings. The impact of co-administration with food/drinks on the solubility of a wide range of drugs should be assessed in order to develop a roadmap which could be used as a risk assessment tool for paediatric drug clinical studies and administration practices.

In vitro dissolution testing conditions that predict the *in vivo* performance are advantageous, especially for the paediatric population for which clinical testing is hindered by ethical and technical considerations. In this project, the factors that could affect drug dissolution were investigated and related to the *in vivo* drug performance. Overall, it is recognised that a deeper knowledge of the paediatric GI environment is still lacking and would assist in refining the predictive biopharmaceutical tools needed to appropriately evaluate formulation performance across age groups.

Regarding the applicability of BCS-based biowaiver criteria into paediatrics, it is evident that a consensus on a paediatric BCS needs to be reached and should address the heterogeneity of the paediatric population and the possible risks of bioinequivalence in vulnerable paediatric populations.

Future work is needed towards conducting clinical studies in paediatric patients in order to obtain more complete information on paediatric biopharmaceutics. This work should evaluate pharmacokinetics (PK), pharmacodynamics (PD), side effects and acceptance of medicines. Future studies should be performed simulating closely the conditions in which patients receive therapy, including practices of medicine co-administration with food and drinks. In addition, although the *in vitro* dissolution approaches described in this study have the potential to provide an alternative to clinical paediatric studies, especially after refinement, a combination of *in vitro* and *in silico* methods would be a stronger approach to ensure the prediction of paediatric drug product behaviour. In this context, the development of more complex *in silico* models for this population, such as physiologically based pharmacokinetic (PBPK) modelling to predict the effects on the PK and PD of the drug, should be explored.

Appendix

Appendix I: Drugs recommended to be mixed with food and drinks, according to the Neonatal and Pediatric Dosage Handbook (1).

Drug	BCS Class	Dosage form	Drug ionisation¥	Aqueous solubility (mg/mL) (2)	Mixed with			Notes
					Drinks	Soft foods	Others	
Abacavir	III (3)	Solution, Tablet	Weak base	1.21			X food	
Abacavir and Lamivudine	-	Tablet	-	-			X food	
Abacavir, Dolutegravir and Lamivudine	-	Tablet	-	-			X food	
Abacavir, Lamivudine and Zidovudine	-	Tablet	-	-			X food	
Acarbose	III (3)	Tablet	Amphoteric	108.0			X meal	
Acetaminophen	I (3)	Caplet	Amphoteric	4.15			X food*	
Acetaminophen and codeine	-	Capsule, Solution, Suspension, Tablet	-	-			X food*	
Acetazolamide	IV (3)	Capsule ER, Tablet, Solution	Amphoteric	2.79			X food*, cherry or chocolate syrup	
Acetylcysteine	I (4)	Solution	Weak acid	5.09	X cola, orange juice, or other soft drink			

Drug	BCS Class	Dosage form	Drug ionisation¥	Aqueous solubility (mg/mL) (2)	Mixed with			Notes
					Drinks	Soft foods	Others	
Acyclovir	III (3)	Capsule, Tablet, Suspension	Amphoteric	2.5			X food*	
Adefovir	III (5)	Tablet	Amphoteric	2.02			X food*	
Albendazole	II (3)	Tablet	Amphoteric	0.0228			X food*	
Albuterol	I (3)	Syrup, Tablet	Amphoteric	-			X food*	
Alcohol (ethyl)	-	Ampoule	Neutral	-	X water, juice			
Allopurinol	I (3)	Tablet	Weak acid	5.88	X fluid		X cherry syrup	
Almotriptan	III (6)	Tablet	Weak base	0.121			X food*	
Aluminium Hydroxide	IV (3)	Capsule, Syrup	Amphoteric	-			X meal	
Amantadine	-	Capsule, Tablet, Syrup	Weak base	6.29			X food*	
Amiloride	III (3)	Tablets	Weak base	1.22	X milk		X food	
Aminocaproic Acid	-	Solution, Tablet, Syrup	Amphoteric	505			X food*	
Amiodarone	II (7)	Tablet	Weak base	0.00476			X meal	Do not administer with grapefruit juice
Amitriptyline	I (3)	Tablet	Weak base	0.0045			X food*	
Amlodipine	III (3)	Tablet	Weak base	0.0753			X food*	
Amoxicillin	I (8)	Tablet	Amphoteric	0.958	X formula, milk, juice			Administer immediately after mixing

Drug	BCS Class	Dosage form	Drug ionisation¥	Aqueous solubility (mg/mL) (2)	Mixed with			Notes
					Drinks	Soft foods	Others	
Amoxicillin and clavunate	-	Tablet, Suspension	-	-	X formula, milk, juice			
Amphetamine	III (3)	Tablet, Suspension	Weak base	1.74			X food*	
Anagrelide	-	Capsule	Weak base	0.279			X food*	
Aprepitant	IV (9)	Capsule	-	0.0194			X food*	
Arginine	-	Powder	Amphoteric	-			X meal	
Aripiprazole	IV (3)	Tablet, Solution, Suspension	Amphoteric	0.00777	X liquid			
Artemether and lumefantrine	-	Tablet	-	-	X water		X meal	Crush tablet and mix with water, followed with food, milk, formula, pudding, porridge or broth
Ascorbic acid	III (3)	Capsule, Powder, Syrup, Tablet	Weak acid	400			X food	
Aspirin	II (10)	Tablet, Caplet	Weak acid	1.46	X water, milk		X food*	
Atazanavir	II (11)	Powder	Amphoteric	0.00327	X beverage[1]	X [2]	X food	[1] *e.g.* milk, water, formula [2] *e.g.* yoghurt or applesauce
Atenolol	III (3)	Tablet	Weak base	13.3			X food	
Atomoxetine	I (3)	Capsule	Weak base	0.0039	X water, liquids		X food	
Atorvastatin	II (3)	Tablet	Weak acid	0.00063			X food	

Drug	BCS Class	Dosage form	Drug ionisation[¥]	Aqueous solubility (mg/mL) (2)	Mixed with			Notes
					Drinks	Soft foods	Others	
Auranofin	-	Capsule	-	0.151			X food	
Azithromycin	II (7)	Tablet	Weak base	0.514			X food	
Baclofen	-	Tablet	Amphoteric	0.712	X milk		X food	
Balsalazide	-	Capsule, Tablet	Weak acid	0.0621		X applesauce (capsule)	X food	
Benazepril	I (3)	Tablet	Amphoteric	0.0022			X food	
Benztropine	-	Tablet	Weak base	0.0012			X food	
Betaine	-	Powder	Weak base	1.56			X food	
Biotin	-	Capsule, Tablet	Weak acid	0.22			X food	
Bosentan	-	Tablet	Amphoteric	0.00904	X non-acidic liquid		X meal	Avoid grapefruit and grapefruit juice
Brivaracetam	-	Tablet	Amphoteric	46.8	X liquid		X food	
Bromocriptine	-	Capsule, Tablet	Amphoteric	0.0858			X food*	
Budesonide	II (4)	Capsule	Neutral	0.0457		X applesauce (capsule)	X meals	
Bumetanide	-	Tablet	Amphoteric	0.0257			X food*	
Bupropion	I (3)	Tablet	Weak base	312			X meal	
Buspirone	I (3)	Tablet	Weak base	0.588			X food*	
Busulfan	-	Tablet	Neutral	69				
Butalbital, Acetaminophen and Caffeine	-	Tablet, Capsule	-	-			X food	
Caffeine	I (12)	Solution, Tablet	Neutral	21.6			X meal	
Calcitrol	-	Capsule	-				X meal	

Drug	BCS Class	Dosage form	Drug ionisation[¥]	Aqueous solubility (mg/mL) (2)	Mixed with			Notes
					Drinks	Soft foods	Others	
Calcium acetate	-	Capsule, Tablet	-	147	X fluids		X meal	
Calcium carbonate	-	Capsule, Tablet, Suspension	-	128	X fluids		X meal	
Calcium citrate	-	Capsule, Tablet, Suspension	-	4.12	X fluids		X food	
Calcium glubionate	-	Syrup	-	47.2	X fluids		X meal	
Calcium gluconate	-	Capsule, Tablet	-	44.2	X fluids		X meal	
Calcium lactate	-	Capsule, Tablet	-	191	X fluids		X meal	
Candesartan	II (3)	Tablet	Amphoteric	0.00667			X meal	
Carbamazepine	II (3)	Chew tablet, suspension, Tablet ER, Capsule ER	Neutral	0.152	X liquid medicinal agents (suspension)	X [1] (capsule)	X food, meal* (tablet)	[1] *e.g.* applesauce
Carvedilol	II (3)	Tablet, Capsule	Amphoteric	0.00444		X applesauce ONLY (ER capsules)	X food (tablet)*	
Castor oil	-	Oil (discontinued)	-	-	X milk, juice, carbonated beverage			
Cefaclor	III (3)	Capsule, suspension	Amphoteric	10			X meal	
Cefadroxil	III (13)	Capsule, Tablet, Suspension	Amphoteric	1.11			X food	
Cefdinir	IV (3)	Capsule, Suspension	Weak acid	0.0878			X food*	
Cefditoren	II (3)	Tablet	Amphoteric	0.0441			X meal	

Drug	BCS Class	Dosage form	Drug ionisation[¥]	Aqueous solubility (mg/mL) (2)	Mixed with			Notes
					Drinks	Soft foods	Others	
Cefixime	IV (3)	Capsule, Tablet, Suspension	Amphoteric	0.0551			X food	
Cefpodoxime	IV (3)	Tablet, Suspension	Amphoteric	0.185			X food (tablet)	
Cefprozil	III (3)	Table, Suspension	Amphoteric	0.055			X food	
Ceftibuten	II (14)	Capsule	Amphoteric	0.0705			X food	
Cefuroxime	IV (3)	Tablet, Suspension	Weak acid	0.284			X food	
Celecoxib	II (3)	Capsule	Weak acid	0.00503		X applesauce	X food (doses < 200 mg) *	
Cephalexin	IV (15)	Capsule, Tablet, Syrup	Amphoteric	1.789			X food	
Cetirizine	III (3)	Capsule, Tablet, Suspension	Amphoteric	0.101			X food	
Charcoal, activated	-	Liquid, Suspension	-	0.0	X orange juice		X chocolate syrup	Avoid adding chemicals, dairy products, syrups (Actidose)
Chenodiol	-	Tablet	Weak acid	0.0899			X food	
Chloral hydrate	-	Capsule (discontinued)	Weak acid	43.4	X water, fruit juice, ginger ale, formula			
Chloroquine	II (3)	Tablet	Weak base	0.0175			X meal, chocolate syrup*	

Drug	BCS Class	Dosage form	Drug ionisation[¥]	Aqueous solubility (mg/mL) (2)	Mixed with			Notes
					Drinks	Soft foods	Others	
Chlorothiazide	IV (16)	Tablet, Suspension	Weak acid	0.398			X food	
Chlorpheniramine	I (3)	Liquid, Tablet, suspension	Weak base	0.0519			X food	
Chlorpromazine	II (3)	Solution, Tablet	Weak base	0.00417	X water, milk		X food	
Chlorthalidone	-	Tablet	Weak acid	0.0528			X food	
Chlorzoxazone	-	Tablet	Weak acid	2.96			X food	
Cholecalciferol	-	Capsule, Liquid, Tablet	Neutral	0.00038			X food	
Choline magnesium trisalicylate	-	Tablet, Liquid	-	-	X milk, fruit juice		X food*	
Cimetidine	III (3)	Solution, Tablet	Amphoteric	0.816			X food	
Ciprofloxacin	III (3)	Tablet, Suspension	Amphoteric	1.35			X food*	Dairy foods reduce absorption
Citalopram	I (3)	Tablet, Solution	Weak base	0.0059			X meal	
Clarithromycin	II (3)	Tablet, Suspension	Weak base	0.0003			X meal, food	
Clemastine	-	Tablet, Syrup	Weak base	0.0004			X food	
Clindamycin	I (4)	Solution, Capsule	Amphoteric	0.031			X meal	
Clobazam	-	Tablet	Neutral	0.164		X applesauce		
Clomipramine	I (17)	Capsule	Weak base	0.014			X food, cherry syrup*	
Clonazepam	-	Tablet	Amphoteric	0.011			X food	
Clonidine	III (3)	Liquid Tablet	Weak base	0.48			X meal	

Drug	BCS Class	Dosage form	Drug ionisation[¥]	Aqueous solubility (mg/mL) (2)	Mixed with			Notes
					Drinks	Soft foods	Others	
Clopidogrel	II (3)	Tablet	Weak base	0.051			X food	
Clorazepate	-	Tablet	Amphoteric	0.025			X food	
Clozapine	II (3)	Tablet, Suspension	Weak base	0.012			X food	
Codeine	III (3)	Tablet, Solution	Amphoteric	0.578			X food	
Colchicine	III (3)	Tablet, Capsule	Neutral	45			X meal	
Colesevelam	-	Granules, Tablet	-	Insoluble	X liquid (tablet)		X meal	
Colestipol	-	Granules, Tablet	-	Insoluble	X beverage, liquid (tablet)		X soups, cereals, pulpy fruits[1]	[1] *e.g.* pineapple, peaches, pears
Cortisone	-	Tablet	Weak acid	0.0278 (acetate)	X milk		X food, meal*	
Cyanocobalamin	III (2)	Liquid, Tablet	-	12.5			X food	
Cycloserine	-	Capsule	Amphoteric	877			X meal	
Cyclosporine	II (4)	Solution	Weak acid	-	X milk, chocolate milk, orange or apple juice			
Danazol	-	Capsule	Amphoteric	0.0176			X fatty meal	
Dantrolene	-	Capsule	Weak acid	0.0805	X juice or liquid			
Darunavir	-	Tablet	-	0.0668			X food	If co-administered with ritonavir, food is required

Drug	BCS Class	Dosage form	Drug ionisation[¥]	Aqueous solubility (mg/mL) (2)	Mixed with			Notes
					Drinks	Soft foods	Others	
Deferasirox	II (4)	Tablet	-	0.0343	X water, other liquids			
Desipramine	-	Tablet	Weak base	0.0396			X food*	
Desloratadine	I (3)	Tablet, Syrup	Weak base	0.00395			X food	
Dexamethasone	III (3)	Tablet, Solution	Weak acid	0.0505	X milk		X food, syrup	
Dexchlor-pheniramine	-	Syrup	-	0.0519			X food	
Dexmethylphenidate	-	Capsule (ER)	-	0.182		X applesauce (ER)	X food	
Dextroamphetamine and amphetamine	-	Capsule, Tablet	-	-		X applesauce (capsule)	X Ora-sweet®α	
Dextromethorphan	-	Capsule, Liquid, Syrup	Weak base	0.00851			X meal	
Diazepam	II (3)	Tablet, Solution	Weak base	0.0122			X food, water	
Diclofenac	II (3)	Tablet, Capsule	Weak acid	0.00447	X milk		X food*	
Diltiazem	I (3)	Capsule (ER)	Weak base	0.0168		X applesauce (ER capsules)		
Dimenhydrinate	-	Tablet	Weak base	0.00125			X food	
Diphenhydramine	-	Capsule, Solution, Syrup, Liquid	Weak base	0.0752			X meal	
Diphenoxylate and atropine	-	Tablet, Solution	-	-			X food*	

Drug	BCS Class	Dosage form	Drug ionisation[¥]	Aqueous solubility (mg/mL) (2)	Mixed with			Notes
					Drinks	Soft foods	Others	
Docusate	-	Liquid, Syrup	Weak acid	-	X milk, fruit juice, formula			
Dolasetron	I (3)	Ampoule, Tablet	Weak base	0.261	X apple, apple-grape juice (solution)		X food (tablet)	
Doxazosin	I (3)	Tablet	Weak base	0.79			X food, meal	
Doxepin	I (19)	Solution	Weak base	0.0319	X water, milk, juice: orange, grapefruit, tomato, prune, pineapple juice			Do not mix with carbonated beverages
Doxycycline	IV (3)	Pellets DR, Capsule, Tablet	Amphoteric	0.63	X fluid. Avoid formula, milk, dairy products	X applesauce (pellets)	X food*	
Dronabinol	-	Capsule	-	2.8			X meal	
Efavirenz	II (4)	Capsule	Weak acid	0.00855	X formula	X[1]		[1]*e.g.* applesauce, grape jelly, yoghurt
Elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide	-	Tablet	-	-			X food	
Elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate	-	Tablet	-	-			X food	
Emtricitabine	I (20)	Capsule, Solution	Weak base	112			X food	

Drug	BCS Class	Dosage form	Drug ionisation¥	Aqueous solubility (mg/mL) (2)	Mixed with			Notes
					Drinks	Soft foods	Others	
Emtricitabine, rilpivirine, and tenofovir alafenamide	-	Tablet	-	-			X meal	
Emtricitabine and Tenofovir disoproxil fumarate	-	Tablet	-	-			X food	
Emtricitabine, rilpivirine and tenofovir disoproxil fumarate	-	Tablet	-	-			X meal (> 500 kcal)	
Enalapril	I (3)	Tablet, Solution	Amphoteric	16.4			X food	
Ephedrine	I (19)	Capsule	Weak base	63.6			X food	
Ergocalciferol	III (13)	Capsule, Solution, Tablet	Neutral	0.05			X meal	
Ergotamine	I (21)	Sublingual tablet	Amphoteric	0.223			X meal	
Ergotamine and caffeine	-	Tablet	-	-			X meal	
Escitalopram	I (22)	Solution, Tablet	-	0.00588			X food	
Esomeprazole	-	Capsule	Amphoteric	0.353		X applesauce		
Estradiol	I (13)	Tablet	Weak acid	0.0213			X food, meal*	
Estrogens	-	Tablet	Weak acid	-			X food*	
Ethacrynic acid	-	Tablet	Weak acid	0.0194	X milk		X food	
Ethambutol	III (23)	Tablet	Weak base	7.58	X apple juice	X applesauce	X food	Do not mix with other juices or syrups (not stable)

Drug	BCS Class	Dosage form	Drug ionisation[¥]	Aqueous solubility (mg/mL) (2)	Mixed with			Notes
					Drinks	Soft foods	Others	
Ethosuximide	III (3)	Capsule Solution	Weak acid	101	X milk		X food*	
Etodolac	II (7)	Capsule, Tablet	Weak acid	0.0392			X food*	
Etoposide	II (7)	Ampoule	Weak acid	0.978	X orange or apple juice, lemonade			
Etravirine	-	Tablet	-	0.0169	X water, milk, orange juice		X meal	Not grapefruit juice or carbonated beverages
Everolimus	IV(3)	Tablet	-	0.00163			X food	
Ezetimibe	II (3)	Tablet	Neutral	0.00846			X meal	
Ezetimibe and Simvastatin	-	Tablet	-	-			X meal	
Famciclovir	III (3)	Tablet	Weak base	-			X food*	
Famotidine	IV (3)	Solution, Tablet, Suspension	Amphoteric	0.271			X food, antacids, Ora-Sweet®α, Ora-Plus®α	
Felbamate	II (7)	Tablet, Suspension	Weak base	0.742			X meal	
Felodipine	II (7)	Tablet	Weak base	0.00715			X light meal	
Ferrous gluconate	-	Tablet	-	-	X water, juice		X food*	Do not administer with milk products
Ferrous sulfate	-	Tablet, Syrup, Solution	-	-	X water, juice		X food*	Do not administer with milk or milk products
Fexofenadine	I (3)	Tablet, Suspension	Amphoteric	0.00266			X food	Avoid administration with fruit juices

Drug	BCS Class	Dosage form	Drug ionisation¥	Aqueous solubility (mg/mL) (2)	Mixed with			Notes
					Drinks	Soft foods	Others	
Flecainide	I (22)	Tablet	Amphoteric	0.0324			X food	Avoid administration with milk or formulas
Fluconazole	III (3)	Tablet, Suspension	Weak base	0.001			X meal	
Fluoxetine	I (3)	Capsule, Tablet, Solution	Weak base	50			X food	
Flurazepam	-	Capsule	Weak base	500			X meal	
Flurbiprofen	II (3)	Tablet	Weak acid	0.0249	X milk		X food, antacids*	
Fluvastatin	II (25)	Capsule, Tablet	Weak acid	0.00046			X meal	
Fluvoxamine	I (3)	Capsule, Tablet	Weak acid	0.00734			X meal	
Folic acid	III (13)	Capsule, Tablet	Amphoteric	0.0016			X meal	
Fosamprenavir	II (4)	Tablet, Suspension	Amphoteric	0.685			X food*	*food in paediatric patients and no food in adults (suspension)
Fosinopril	-	Tablet	Weak acid	0.00101			X food	
Furosemide	IV (3)	Tablet	Weak acid	0.118	X milk		X food	
Gabapentin	III (4)	Capsule	Amphoteric	4.34	X[1]	X[2]		[1]*e.g.* orange juice [2]*e.g.* applesauce
Glycopyrrolate	-	Tablet	Weak base	0.000944			X meal	
Guaifenesin	-	Tablet, Liquid	Neutral	14.9	X fluid (large amount)			

Drug	BCS Class	Dosage form	Drug ionisation[¥]	Aqueous solubility (mg/mL) (2)	Mixed with			Notes
					Drinks	Soft foods	Others	
Guaifenesin and codeine	-	Tablet, Liquid, Capsule	-	-	X fluid (large amount)		X food*	
Guaifenesin and dextromethorphan	-	Tablet, Liquid, Syrup	-	-	X fluid (large amount)			
Haloperidol	II (3)	Tablet, Solution	Amphoteric	0.00446	X water, acidic beverage, milk*		X food *	Do not mix with coffee or tea
Hydralazine	III (3)	Tablet	Weak base	2.61			X food	
Hydro-chlorothiazide	III (26)	Tablet, Capsule	Weak acid	2.24	X milk		X food	
Hydrocodone and acetaminophen	-	Tablet, Capsule, Solution	-	-	X milk		X food*	
Hydrocodone and chlorpheniramine	-	Capsule	-	-			X meal	
Hydrocortisone	-	Tablet	Neutral	0.199	X milk		X food*	
Hydromorphone	-	Capsule	Amphoteric	4.39	X milk (IR)		X food (IR)*	
Hydroxyzine	II (3)	Tablet, Capsule, Solution, Syrup	Weak base	700			X food	
Hyoscyamine, atropine, scopolamine and phenobarbital	-	Tablet	-	-			X meal	
Ibuprofen	II (3)	Tablet, Capsule, Suspension	Weak acid	0.0684	X milk		X food*	

Drug	BCS Class	Dosage form	Drug ionisation[¥]	Aqueous solubility (mg/mL) (2)	Mixed with			Notes
					Drinks	Soft foods	Others	
Imatinib	II (4)	Tablet	Weak base	0.0146	X water, apple juice[1]		X meal	[1]50 mL -100 mg tablet 200 mL -400 mg tablet
Imipramine	I (13)	Tablet, Capsule	Weak base	0.0182			X food*	
Indinavir	IV (26)	Capsule	Amphoteric	0.015	X water, liquids[1]		X light snack[2]	[1]*e.g.* skim milk, coffee, tea, juice [2] *e.g.* dry jelly toast, cornflakes w/ skim milk
Indomethacin	II (7)	Capsule, Suspension	Weak acid	0.937	X milk		X food, antacids*	
Iodoquinol	-	Tablets	Amphoteric	0.0815		X applesauce	X chocolate syrup	
Irbesartan	II (3)	Capsule	Amphoteric	0.00884		X applesauce (capsules)	X food	
Irinotecan	-	Ampoule	Amphoteric	0.11	X cranberry grape juice			
Isotretinoin	II (3)	Capsule	Weak acid	0.00477	X liquid		X meal	
Isradipine	-	Capsule, Tablet	Weak base	0.23			X meal	
Itraconazole	II (3)	Capsule	Weak base	0.00964			X food	
Ivacaftor	-	Granules	-	0.002	X water, milk, juice	X[1]		[1]*e.g.* pureed fruit/vegetable, applesauce, yoghurt Mix should be consumed within 1 hour
Ketamine	I (27)	Ampoule	Weak base	0.046	X cola, cherry juice, other beverages			

Drug	BCS Class	Dosage form	Drug ionisation[¥]	Aqueous solubility (mg/mL) (2)	Mixed with			Notes
					Drinks	Soft foods	Others	
Ketoconazole	II (7)	Tablet	Weak base	$8.66*10^{-5}$	X acidic liquid[1]			[1]*e.g.* soda pop
Ketorolac	I (19)	Tablet	Weak acid	2.5 (salt)	X milk		X food*	
Labetalol	I (13)	Tablet	Amphoteric	0.117			X meal, cherry syrup	
Lacosamide	I (28)	Solution, Tablet	-	0.465			X food	
Lactobacillus	-	Granules, Capsules, Powder	-	-	X milk, fruit juice, water		X cereal, food	
Lactulose	II (4)	Solution	Weak acid	792	X milk, fruit juice, water			
Lamivudine	III (3)	Tablet	Weak base	70			X meal	
Lamivudine and Zidovudine	-	Tablet	-	-			X meal	
Lamotrigine	II (3)	Dispersible tablet	Weak base	0.488	X water, diluted fruit juice		X meals	
Lansoprazole	II (7)	Capsule	Amphoteric	0.00097	X apple juice, orange juice, tomato juice[1]	X applesauce, ensure pudding, cottage cheese, yoghurt or strained pears[2]		[1]60 mL [2]1 *tbs*
Letrozole	I (29)	Tablet	Weak base	0.0799			X meal	
Levetiracetam	III (3)	Tablet	Neutral	298	X liquid			

Drug	BCS Class	Dosage form	Drug ionisation[¥]	Aqueous solubility (mg/mL) (2)	Mixed with			Notes
					Drinks	Soft foods	Others	
Levocarnitine	-	Solution	Amphoteric	2500	X beverages, liquid food			
Levocetirizine	III (22)	Tablet, Solution	Amphoteric	0.0658			X food	
Levofloxacin	I (3)	Tablet	Amphoteric	1.44			X food	
Levothyroxine	I (3)	Tablet	Amphoteric	0.105	X breast milk, formula[1], water*		X food	[1]non-soy
Linezolid	IV (3)	Tablet, Suspension	Amphoteric	3			X food	
Lisdexamfetamine	-	Capsule	-	792			X food	
Lisinopril	III (13)	Tablet	Amphoteric	97			X food	
Lithium	I (26)	Tablet, Suspension, Capsule	Weak acid	-			X meal*	
Lopinavir and ritonavir	-	Tablet, Solution	-	-			X food[1]	[1]Adm with sweet foods, chocolate syrup, or peanut butter to help mask taste
Loratadine	II (15)	Tablet, Capsule, Syrup, Solution	Weak base	0.000011			X meal	
Lorazepam	I (22)	Solution	Amphoteric	0.08	X water, juice, soda	X[1]	X food*	[1] *e.g.* applesauce, pudding
Losartan	I (13)	Tablet	Amphoteric	0.00082			X food	

Drug	BCS Class	Dosage form	Drug ionisation[¥]	Aqueous solubility (mg/mL) (2)	Mixed with			Notes
					Drinks	Soft foods	Others	
Magnesium-aspartate hydrochloride	-	Granules	-	-	X water, juice			
Magnesium sulfate	-	Granules	-	710	X lemon juice			
Maraviroc	III (30)	Tablet	Weak base	0.00883			X meal	
Mebendazole	II (3)	Tablet	Amphoteric	0.0713			X food	
Meclizine	II (22)	Tablet	Weak base	0.001			X food*	
Medium chain triglycerides	-	Emulsion oil	-	-	X water, other beverage (*e.g.* juice, milk)		X sauces, salad dressings, other foods	
Medroxy-progesterone	IV (20)	Tablet	Neutral	0.0021			X food	
Mefloquine	II (4)	Tablet	Amphoteric	0.038	X water, milk, chocolate syrup	X applesauce, jelly	X food	
Megestrol	II (25)	suspension	Neutral	0.00336			X food	
Meloxicam	IV (22)	Tablet, Capsule, Suspension	Weak acid	0.00715	X milk		X food*	
Mesalamine	IV (4)	Capsule	Amphoteric	0.84		X yoghurt or peanut butter[1]	X food with a pH < 6	[1]Pentasa®
Metformin	III (4)	Tablet	Weak base	1.38			X meal*	

Drug	BCS Class	Dosage form	Drug ionisation[¥]	Aqueous solubility (mg/mL) (2)	Mixed with			Notes
					Drinks	Soft foods	Others	
Methadone	I (31)	Tablet, Solution	Weak base	0.0059	X juice, water			
Methenamine	-	Tablet	Weak base	766	X cranberry juice*		X food*	
Methsuximide	-	Capsule	Neutral	2.13			X food	
Methyldopa	III (3)	Tablet	Amphoteric	10			X food	
Methylphenidate	I (4)	Tablet, Capsule	Weak base	1.25	X water, milk or juice [1]	X applesauce [2]		[1]Concerta®, Metadate® [2]Metadate®, Ritaline LA®
Methylprednisolone	-	Tablet	Weak acid	0.120	X milk		X food	Not grapefruit juice
Metolazone	-	Tablet	Weak acid	0.06			X food*, cherry syrup, Ora-Sweet®α, Ora-Plus®α	
Metronidazole	IV (3)	Tablet Capsule	Weak base	4.5			X food*, Ora-Sweet®α, Ora-Plus®α	
Metyrapone	-	Capsule	Weak base	0.427	X milk *	Yoghurt	X food*	
Mexiletine	I (3)	Capsule	Weak base	8.25	X milk		X food*	
Mineral oil	-	suspension	-	Not soluble	X milk, water		X cocoa	
Minoxidil	III (13)	Tablet	Weak base	2.2			X food	
Mitotane	-	Tablet	Neutral	0.0001			X MCT oil, then solution mixed with a fatty food (milk or yoghurt)	

Drug	BCS Class	Dosage form	Drug ionisation¥	Aqueous solubility (mg/mL) (2)	Mixed with			Notes
					Drinks	Soft foods	Others	
Modafinil	IV (3)	Tablet	Neutral	0.622			X food	
Montelukast	II (4)	Granules	Amphoteric	$8.2*10^{-6}$	X baby formula or breast milk[1]	X applesauce, ice cream[2]	X rice, carrots	[1] 5 mL [2] a spoonful Cold or at room temp.
Morphine	I (4)	Capsule (ER)	Amphoteric	0.149		X applesauce	X food	
Nadolol	III (19)	Tablet	Weak base	8.33			X meal	
Naproxen	II (7)	Tablet, suspension	Weak acid	0.0159	X milk		X food, antacids*	
Nefazodone	-	Tablet	Weak base	0.0698			X food	
Nelfinavir	II (3)	Tablet	Amphoteric	0.00191			X food	
Neostigmine	I (3)	Tablet	Weak base	0.0677			X food	
Nevirapine	II (3)	Tablet	Weak base	0.0007	X milk, water or soda (IR)		X meal	
Niacin	III (3)	Tablet, Capsule, Powder	Amphoteric	18	X milk		X food*, low fat snack	
Nicardipine	I (3)	Capsule	Weak base	0.0022			X meals	Avoid high fat meals
Nifedipine	II (3)	Capsule	Weak base	0.0177			X food	
Nitisinone	-	Capsule	Weak acid	0.00811	X water, formula	X applesauce		
Nitrofurantoin	IV (3)	suspension	Weak base	0.0795	X water, milk*, fruit juice, or formula		X food	

Drug	BCS Class	Dosage form	Drug ionisation[¥]	Aqueous solubility (mg/mL) (2)	Mixed with			Notes
					Drinks	Soft foods	Others	
Nizatidine	III (3)	Tablet, Capsule	Weak base	0.039	X [1] (capsule)		X food (tablet)	[1] Lemon-lime Gatorade®, Ocean- Spray® Cran-Grape juice, V8®100% vegetable juice Do not administer or mix with apple juice
Norethindrone	I (3)	Tablet	Neutral	0.0069			X food	
Nortriptyline	I (22)	Capsule, Solution	Weak base	0.00087			X food	
Olanzapine	I (4)	Tablet	Weak base	0.0942			X food	
Olmesartan	II (32)	Tablet	Weak base	0.0105			X food	
Omeprazole	II (4)	Capsule	Amphoteric	0.359		X applesauce		
Ondansetron	I (3)	Tablet, Solution	Weak base	0.248			X food, cherry syrup, Ora-Sweet®α, Ora-Plus®α	
Oseltamivir	III (3)	Capsule	Amphoteric	0.686	X food, sweetened liquid [1]			[1] *e.g.* chocolate syrup, corn syrup, caramel topping, light brown sugar dissolved in water
Oxaprozin	II (7)	Tablet	Weak acid	0.0325	X milk		X food*	
Oxcarbazepine	IV (3)	Tablet, Suspension	Neutral	0.308			X meal	
Oxybutynin	I (3)	Tablet, Syrup, Capsule	Amphoteric	0.01	X liquid (capsules)		X food	
Oxycodone	IV (3)	Tablet, Capsule, Solution	Amphoteric	5.59			X food*	

Drug	BCS Class	Dosage form	Drug ionisation[¥]	Aqueous solubility (mg/mL) (2)	Mixed with			Notes
					Drinks	Soft foods	Others	
Oxycodone and acetaminophen	-	Tablet, Capsule, Solution	-	-	X milk		X food*	
Oxycodone and aspirin	-	Tablet	-	-	X milk		X food*	
Paliperidone	II (33)	Tablet	Weak base	0.297	X liquids (ER tablets)			
Pancrelipase	-	Tablet, Capsule	-	1	X liquid, water, or juice	X small amount of acidic food (pH ≤ 4.5) [1]	X snacks, meal	[1]*e.g.* applesauce, prepared baby food Infants: avoid mixing with breast milk or formula.
Pantoprazole	III (22)	suspension (DR)	Amphoteric	0.495	X apple juice[1]	X applesauce[2]		[1]5 mL; [2]1 tbs Do not administer with other liquids or foods
Paricalcitol	-	Capsule	Neutral	0.0068			X food	
Paromomycin	-	Capsule	Amphoteric	79.7			X meal	
Paroxetine	I (3)	Capsule, Tablet, suspension	Weak base	0.00853			X meal*	
Penicillamine	III (3)	Capsule	Amphoteric	111	X fruit juice	X chilled puree fruit		
Penicillin V Potassium	III (19)	Tablet, Solution	Weak acid	0.454			X food*	
Pentobarbital	-	Ampoule	Weak acid	6.78			X cherry syrup	
Pentoxifylline	-	Tablet	Neutral	77			X food or antacids*	
Perampanel	-	Tablet, Suspension	-	0.0056			X meal	
Perphenazine	-	Tablet	Weak base	0.0283			X meal*	

Drug	BCS Class	Dosage form	Drug ionisation[¥]	Aqueous solubility (mg/mL) (2)	Mixed with			Notes
					Drinks	Soft foods	Others	
Phenazopyridine	II (7)	Tablet	Weak base	0.202			X food*	
Phenobarbital	I (19)	Solution	Weak acid	1.1	X water, milk or juice			
Phenoxybenzamine	-	Capsule	Weak base	0.0103	X milk*			
Phenytoin	II (3)	Capsule (ER)	Weak acid	0.032			X meal	
Phytonadione	-	Tablet	Neutral	5.92e05			X food	
Pimozide	II (3)	Tablet	Amphoteric	0.01			X meal	
Piroxicam	II (7)	Capsule	Amphoteric	0.023	X milk		X food*	
Posaconazole	II (34)	Tablet	Amphoteric	0.012			X food (DR tablets)	
Potassium chloride	I (22)	Powder, Capsule, Solution	Neutral	357	X water, juice or other beverage[1] (powder) Juice, water (solution)	X applesauce or pudding[2] (capsule)		6 ounces [2]1 tbs
Potassium citrate and citric acid	-	Powder	-	-	X water or juice[1]			[1]at least 6 ounces
Potassium iodide	I (4)	Solution	Neutral	1428.6	X [1]:water, milk, broth, fruit juice; formula, soda, orange juice, milk		X[2]: Raspberry syrup	[1] SSKI® [2] Iosat®, Thyrosafe®
Potassium iodide and iodine	-	Solution	-	-	X water, fruit juice or milk			

Drug	BCS Class	Dosage form	Drug ionisation¥	Aqueous solubility (mg/mL) (2)	Mixed with			Notes
					Drinks	Soft foods	Others	
Potassium phosphate and sodium phosphate	-	Tablet Powder	-	-	X juice (powder)		X food (tablet)	
Pravastatin	III (3)	Tablet	Weak acid	0.242			X meal	
Prazosin	I (26)	Capsule	Weak base	0.5			X meal	
Prednisolone	I (35)	Tablet, Solution, Suspension	Weak acid	0.223	X milk		X food, meal*	
Prednisone	I (36)	Tablet, Solution	Weak acid	0.111	X milk		X food*	
Primaquine	I (21)	Tablet	Weak base	0.0564			X food*	
Primidone	II (7)	Tablet	Weak acid	0.5			X food*	
Probenecid	-	Tablet	Weak acid	0.021			X food*	
Prochlorperazine	II (21)	Tablet	Weak base	0.015	X water		X food	
Promethazine	I (26)	Tablet, Syrup, Solution	Weak base	0.0156	X milk, water		X food*	
Promethazine and phenylephrine	-	Syrup	-	-	X milk, water		X food	
Promethazine, phenylephrine and codeine	-	Syrup	-	-	X water		X food*	
Propranolol	I (3)	Solution, Capsule	Neutral	0.0617	X water, fruit juice, liquid (oral solution)	X semi solid food (oral solution)	X food (ER capsules)	
Protriptyline	-	Tablet	Weak base	0.00104			X food*	Do not administer with grapefruit juice

Drug	BCS Class	Dosage form	Drug ionisation[¥]	Aqueous solubility (mg/mL) (2)	Mixed with			Notes
					Drinks	Soft foods	Others	
Pseudoephedrine	III (3)	Tablet, Syrup, Liquid	Amphoteric	0.007	X milk*, water			
Pseudoephedrine and ibuprofen	-	Tablet, Capsule	-	-			X food	
Psyllium	-	Granules, Powder	-	-	X water or juice[1]			[1] 8 ounces
Pyrantel pamoate	-	Tablet	Weak acid	0.118	X milk or fruit juice			
Pyridoxine	III (3)	Capsule, Tablet	Amphoteric	220			X meal	
Pyrimethamine	IV (26)	Tablet	Weak base	0.121			X meal	
Quetiapine	II (3)	Tablet	Weak base	0.0403			X light meal	
Quinapril	I (3)	Tablet	Amphoteric	0.001			X food	
Quinidine	I (26)	Tablet	Amphoteric	0.140	X milk		X food*, cherry syrup, Ora-Sweet®α, Ora-Plus®α	
Rabeprazole	III (3)	Capsule	Amphoteric	0.336	X liquid	X		[1] *e.g.* formula, apple juice, paediatric electrolyte solution (small amount) [2] *e.g.* applesauce, fruit or vegetable-based baby food, yoghurt (small amounts)
Raltegravir	II (37)	Tablet	Weak acid	-			X meal	

Drug	BCS Class	Dosage form	Drug ionisation¥	Aqueous solubility (mg/mL) (2)	Mixed with			Notes
					Drinks	Soft foods	Others	
Ranitidine	III (3)	Tablet, Syrup, Capsule	Weak base	24.7			X food, meal	
Ribavirin	III (3)	Tablet, Capsule, Solution	Neutral	33.2			X food	
Riboflavin	I (26)	Tablet, Capsule	Weak acid	0.0847			X food	
Rifabutin	II (38)	Capsule	Amphoteric	0.19		X applesauce		
Rifampicin	II (3)	Capsule	Amphoteric	1.4		X applesauce or jelly		
Rifaximin	IV (39)	Tablet	Amphoteric	0.00738			X food	
Rimantadine	-	Tablet	Weak base	50 (hydrochloride salt)			X food	
Risperidone	II (4)	Solution	Weak base	2.33	X water, coffee, orange juice, or low-fat milk			Do not mix with coffee or tea
Ritonavir	IV (4)	Liquid	Amphoteric	0.00126	X milk, chocolate milk	X vanilla/ chocolate pudding, ice cream	X nutritional supplement	Other techniques: dulling the taste buds by chewing ice, giving popsicles of partially frozen orange or grapefruit concentrates, coating the mouth with peanut butter, administration of strong-tasting foods immediately after a dose.

Drug	BCS Class	Dosage form	Drug ionisation[¥]	Aqueous solubility (mg/mL) (2)	Mixed with			Notes
					Drinks	Soft foods	Others	
Rosiglitazone	I (3)	Tablet	Amphoteric	0.038			X meal	
Rosuvastatin	III (40)	Tablet	Amphoteric	0.0886			X food	
Rufinamide	II (41)	Tablet	Neutral	0.642			X food	
Sacrosidase	-	Solution	-	-	X water, milk, formula			
Sapropterin	III (42)	Powder, Tablet	Amphoteric	20 (dichloride salt)	X water, apple juice, formula	X (powder)		[2]applesauce or pudding (small amount)
Saquinavir	I (3)	Capsule	Amphoteric	0.00765		X jam[2]	X sugar or sorbitol syrup	[1] 3 teaspoons [2] 15 mL
Senna	-	Syrup	-	-	X juice or milk	X ice cream		
Sertraline	I (4)	Solution	Weak base	0.0035	X water, orange juice, lemonade, ginger ale or lemon/lime soda			Do not administer with grapefruit juice
Sildenafil	I (3)	Tablet, Suspension	Amphoteric	3.5			X meal	
Simethicone	-	Tablet, Suspension, Capsule	-	1.71	X water, formula, liquids			
Simvastatin	II (43)	Tablet	Neutral	0.0122			X meal	

Drug	BCS Class	Dosage form	Drug ionisation¥	Aqueous solubility (mg/mL) (2)	Mixed with			Notes
					Drinks	Soft foods	Others	
Sirolimus	II (4)	Solution	Weak acid	0.00173	X water, orange juice			
Sodium phenylbutyrate	-	Powder	-	18	X		X food, meal or feeding	Avoid mixing with acidic beverages
Sodium phosphate	-	Tablet	-	121	X clear liquids[1]			[1] water, flavoured water, pulp-free lemonade, ginger ale or apple juice (8 ounces)
Sodium polystyrene sulfonate	-	Powder	-	-			X syrup	Do not mix with orange juice
Sotalol	I (13)	Solution, Tablet	Amphoteric	5.51			X meal	
Spironolactone	II (3)	Tablet	Neutral	0.022			X food	
Stavudine	I (26)	Capsule	Weak acid	40.5			X food	
Succimer	-	Capsule	Weak acid	2.43	X fruit juice	X[1]		[1]small amount
Sulfamethoxazole and trimethoprim	-	Tablet, Suspension	-	-			X meal	
Sulindac	-	Tablet	Weak acid	3	X milk		X food	
Sumatriptan	III (3)	Tablet	Amphoteric	21.4	X water, other fluids			
Tamoxifen	II (3)	Tablet, Solution	Weak base	0.00102			X food	
Tamsulosin	I (3)	Capsule	Amphoteric	0.0066	X juice	X[1]		[1]yoghurt or pudding
Temozolomide	I (3)	Capsule	Weak base	5.09	X apple juice	X applesauce		
Tenofovir disoproxil fumarate	III (4)	Powder	Weak base	13.4		X applesauce, baby food, yoghurt [1]	X food	[1] 2-4 ounces Do not mix with liquids
Terazosin	-	Capsule	Weak base	29.7			X meal	

Drug	BCS Class	Dosage form	Drug ionisation[¥]	Aqueous solubility (mg/mL) (2)	Mixed with			Notes
					Drinks	Soft foods	Others	
Terbinafine	I (3)	Granules	Weak base	0.0007		X non-acidic food [1]		[1] pudding, mashed potatoes. Do not use fruit-based foods
Terbutaline	-	Tablet	Amphoteric	213			X meal	
Theophylline	I (4)	Capsule	Weak base	7.36		X		
Thiamine	III (3)	Tablet, Capsule	Weak base	500			X food	
Thioridazine	-	Solution, Tablet	Weak base	$3.36*10^{-5}$	X water*[1], milk*, juice[1]		X food*	[1]oral concentrate
Thiothixene	-	Capsule	Weak base	0.0139	X water		X food	
Tiagabine	-	Tablet	Amphoteric	0.0211			X food	
Tinidazole	-	Tablet	Weak base	3.03			X food*, cherry syrup	
Tolmetin	-	Tablet, Capsule	Weak acid	0.222	X milk		X food, antacids*	
Tolterodine	I (3)	Tablet, Capsule	Amphoteric	0.00534			X food	
Topiramate	III (4)	Capsule	Weak acid	9.8		X applesauce, ice cream, pudding, custard, yoghurt, or oatmeal		[1] 1 *tbs*
Topotecan	-	Capsule, Ampoule	Amphoteric	1	X acidic medium[1]			[1]*e.g.* apple, grape or orange juice (30 mL)
Torsemide	-	Tablet	Weak acid	0.0596			X meal	
Tramadol	I (3)	Capsule, Tablet, Suspension	Weak base	0.75			X food	

Drug	BCS Class	Dosage form	Drug ionisation[¥]	Aqueous solubility (mg/mL) (2)	Mixed with			Notes
					Drinks	Soft foods	Others	
Tranexamic acid	I (44)	Tablet	Amphoteric	167			X meal	
Tretinoin	-	Capsule	Weak acid	0.0048	X warm milk	X[1]	X meal	[1]one spoonful
Triamterene	II (3)	Capsule	Weak base	0.0482			X food*	
Trifluoperazine	-	Tablet	Weak base	0.0122			X food*	
Trimethobenzamide	-	Capsule	Weak base	0.04			X food	
Trimethoprim	IV (3)	Tablet, Solution	Weak base	0.400	X milk		X food*	
Ursodiol	II (43)	Tablet, Capsule	Weak acid	0.02			X food, Ora-Sweet®α, Ora-Plus®α	
Valacyclovir	III (43)	Tablet	Amphoteric	3.55			X food	
Valganciclovir	III (45)	Tablet	Amphoteric	4.79			X meal	
Valproic acid and derivatives	II (3)	Capsule	Weak acid	1.3 (valproic acid)		X[1]	X food*	[1]*e.g.* pudding, applesauce (small amount) Do not administer with carbonated drinks
Valsartan	II (3)	Tablet	Weak acid	0.0234			X food	
Vancomycin	-	Solution	Amphoteric	0.225			X flavouring syrup	
Venlafaxine	I (3)	Tablet, Capsule	Weak base	572 (hydrochloride salt)		X applesauce (capsule)	X food	

Drug	BCS Class	Dosage form	Drug ionisation[¥]	Aqueous solubility (mg/mL) (2)	Mixed with			Notes
					Drinks	Soft foods	Others	
Verapamil	II (3)	Capsule	Weak base	0.00447		X applesauce[1] (capsules[2])	X food (tablet, caps), cherry syrup, Ora-Sweet®α, Ora-Plus®α	[1]1 *tbs* [2]only 2 of the commercial formulations
Vigabatrin	I (4)	Tablet	Amphoteric	55.1			X food	
Vitamin A	-	Capsule	Neutral	0.00067	X milk		X food	
Vitamin E	-	Capsule, Tablet, Solution	Neutral	$7.04E^{-6}$			X food	
Warfarin	I (46)	Tablet	Weak acid	0.017			X food	
Zinc sulfate	-	Capsule, Tablet	-	-			X food*	
Ziprasidone	II (47)	Capsule	Weak base	0.00718			X food	
Zonisamide	-	Capsule	Weak acid	0.8			X meal	

■ Drug included in the UK formularies but without recommendations of medicine co-administration with vehicles
■ Drug included in both the UK formularies and the Lexicomp Handbook with recommendations for medicine co-administration with vehicles
(underlined) Recommendations are to mix '*with or without food/meals'* or *'without regards to food/meals'*
[¥] Calculated using Advanced Chemistry Development (ACD/Labs) Software V11.02 (© 1994-2016 ACD/Labs)
* To avoid GI distress α for extemporaneous preparations
ER: Extended release DR: Delayed release
Tbs: tablespoon mL: millilitre

References

1. Taketomo CK, Hodding JH, Kraus DM. Pediatric & neonatal dosage handbook: an extensive resource for clinicians treating pediatric and neonatal patients. 23rd ed. Hudson, Ohio: Lexicomp; 2017.

2. Wishart DS, Knox C, Guo AC, Cheng D, Shrivastava S, Tzur D, et al. DrugBank: a knowledgebase for drugs, drug actions and drug targets. Nucleic Acids Res. 2008;36(suppl 1):D901-D6.

3. Drug Delivery Foundation. BCS database. 2015. http://www.tsrlinc.net/search.cfm. Assessed 5 November 2018.

4. Martir J, Flanagan T, Mann J, Fotaki N. Recommended strategies for the oral administration of paediatric medicines with food and drinks in the context of their biopharmaceutical properties: a review. J Pharm Pharmacol. 2017;69(4):384-97.

5. Dave VS, Gupta D, Yu M, Nguyen P, Varghese Gupta S. Current and evolving approaches for improving the oral permeability of BCS Class III or analogous molecules. Drug Dev Ind Pharm. 2017;43(2):177-89.

6. Informe Público de Evaluación: Almotriptan Cinfa 12.5 MG Comprimidos. 2013. https://cima.aemps.es/cima/pdfs/ipe/78686/IPE_78686.pdf [spanish]. Accessed 6 January 2019.

7. Selvamuthukumar S, Anandam S, Krishnamoorthy K, Rajappan M. Nanosponges: A novel class of drug delivery system-review. J Pharm Pharm Sci. 2012;15(1):103-11.

8. Thambavita D, Galappatthy P, Mannapperuma U, Jayakody L, Cristofoletti R, Abrahamsson B, et al. Biowaiver monograph for immediate-release solid oral dosage forms: amoxicillin trihydrate. J Pharm Sci. 2017;106(10):2930-45.

9. Georgaka D, Butler J, Kesisoglou F, Reppas C, Vertzoni M. Evaluation of dissolution in the lower intestine and its impact on the absorption process of high dose low solubility drugs. Mol Pharm. 2017;14(12):4181-91.

10. Bamigbola EA. Correlation of in vitro dissolution profiles with in vivo pharmacokinetic parameters of some commercial brands of aspirin tablets marketed in Nigeria. Readings in Advanced Pharmacokinetics-Theory, Methods and Applications: InTech; 2012.

11. European Medicines Agency. Assessment report Atazanavir Mylan. 2016. https://www.ema.europa.eu/documents/assessment-report/atazanavir-mylan-epar-public-assessment-report_en.pdf. Accessed 2 February 2019.

12. Smetanova L, Stetinova V, Kholova D, Kvetina J, Smetana J, Svoboda Z. Caco-2 cells and Biopharmaceutics Classification System (BCS) for prediction of transepithelial transport of xenobiotics (model drug: caffeine). Neuroendocrinol Lett. 2009;30:101-5.

13. Chatzizacharia K, Hatziavramidis D. New frames of reference for mapping drugs in the four classes of the BCS and BDDCS into regions with clear boundaries. AICHE J. 2015;61(11):3570-9.

14. Oral drug absorption: Prediction and assessment. Dressman JB, Lennernas H, editors. New York: CRC Press; 2000.

15. Shawahna R. Pediatric biopharmaceutical classification system: using age-appropriate initial gastric volume. AAPS J. 2016;18(3):728-36.

16. Sanphui P, Devi VK, Clara D, Malviya N, Ganguly S, Desiraju GR. Cocrystals of hydrochlorothiazide: solubility and diffusion/permeability enhancements through drug–coformer interactions. Mol Pharm. 2015;12(5):1615-22.

17. Papich MG, Martinez MN. Applying biopharmaceutical classification system (BCS) criteria to predict oral absorption of drugs in dogs: challenges and pitfalls. AAPS J. 2015;17(4):948-64.

18. Vora C, Patadia R, Mittal K, Mashru R. Preparation and characterization of dipyridamole solid dispersions for stabilization of supersaturation: effect of precipitation inhibitors type and molecular weight. Pharm Dev Technol. 2016;21(7):847-55.

19. Khojasteh SC, Wong H, Hop CECA. Oral Absorption. Drug Metabolism and Pharmacokinetics Quick Guide. New York, NY: Springer New York; 2011. p. 47-56.

20. Plöger GF, Hofsäss MA, Dressman JB. Solubility Determination of Active Pharmaceutical Ingredients Which Have Been Recently Added to the List of Essential Medicines in the Context of the Biopharmaceutics Classification System–Biowaiver. J Pharm Sci. 2018;107(6):1478-88.

21. Shawahna R, Rahman N. Evaluation of the use of partition coefficients and molecular surface properties as predictors of drug absorption: a provisional biopharmaceutical classification of the list of national essential medicines of Pakistan. Daru. 2011;19(2):83.

22. Intra-Agency Agreement Between the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the U.S. Food and Drug Administration (FDA) Oral Formulations Platform—Report 1. 2011. http://bpca.nichd.nih.gov/collaborativeefforts/initiatives/upload/Formulations_Table_for_Web_11-02-11.pdf. Accessed 20 February 2016.

23. Becker C, Dressman J, Amidon G, Junginger H, Kopp S, Midha K, et al. Biowaiver monographs for immediate release solid oral dosage forms: Ethambutol dihydrochloride. J Pharm Sci. 2008;97(4):1350-60.

24. Nechipadappu SK, Trivedi DR. Pharmaceutical salts of ethionamide with GRAS counter ion donors to enhance the solubility. Eur J Pharm Sci. 2017;96:578-89.

25. Li Y, Song CK, Kim MK, Lim H, Shen Q, Lee DH, et al. Nanomemulsion of megestrol acetate for improved oral bioavailability and reduced food effect. Arch Pharm Res. 2015;38(10):1850-6.

26. World Health Organisation: Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms (Annex 8) - WHO Technical Report Series, No. 937. 2006. http://apps.who.int/prequal/info_general/documents/TRS937/WHO_TRS_937__annex8_eng.pdf. Accessed 2 March 2016.

27. Clinical Pharmacology Review: Surge Dose® ketamine as an oral analgesic and sedative agent. 2012. http://www.imaginot.com.au/downloads/d8a8979b-750a-45d0-bd31-c97a81bcd049.pdf. Accessed 2 February 2019.

28. European Medicines Agency. Assessment report for vimpat. 2008. https://www.ema.europa.eu/documents/assessment-report/vimpat-epar-public-assessment-report_en.pdf. Accessed 02 February 2019.

29. Australian Product Information: Apo-Letrozole (Letrozole). 2018. http://www.medicines.org.au/files/txpletro.pdf. Accessed 10 January 2019.

30. European Medicines Agency. Assessment report for celsentri. 2017. https://www.ema.europa.eu/documents/variation-report/celsentri-h-c-000811-x-0046-g-epar-assessment-report-variation_en.pdf. Accessed 5 January 2019.

31. Medicines Evaluation Board in the Netherlands. Public assessment report of methadone (as hydrochloride). 2010. https://db.cbg-meb.nl/Pars/h34508.pdf. Accessed 9 January 2019.

32. Thakkar HP, Patel BV, Thakkar SP. Development and characterization of nanosuspensions of olmesartan medoxomil for bioavailability enhancement. J Pharm Bioallied Sci. 2011;3(3):426.

33. Sherje AP, Londhe V. Ternary inclusion complex of paliperidone with β-cyclodextrin and hydrophilic polymer for solubility and dissolution enhancement. J Pharm Innov. 2015;10(4):324-34.

34. Gubbins PO, Krishna G, Sansone-Parsons A, Penzak SR, Dong L, Martinho M, et al. Pharmacokinetics and safety of oral posaconazole in neutropenic stem cell transplant recipients. Antimicrob Agents Chemother. 2006;50(6):1993-9.

35. Vogt M, Derendorf H, Krämer J, Junginger H, Midha K, Shah V, et al. Biowaiver monographs for immediate release solid oral dosage forms: Prednisolone. J Pharm Sci. 2007;96(1):27-37.

36. Vogt M, Derendorf H, Kramer J, Junginger HE, Midha KK, Shah VP, et al. Biowaiver monographs for immediate release solid oral dosage forms: prednisone. J Pharm Sci. 2007;96(6):1480-9.

37. Date AA, Destache CJ. A review of nanotechnological approaches for the prophylaxis of HIV/AIDS. Biomaterials. 2013;34(26):6202-28.

38. Benet LZ, Broccatelli F, Oprea TI. BDDCS applied to over 900 drugs. AAPS J. 2011;13(4):519-47.

39. Danish M, Shetsandi A, Bhise KS. Formulation development and taste masking of rifaximin nanosuspension. Inventi Rapid: Pharm Tech. 2013.

40. Medicines & Healthcare products Regulatory Agency. Public assessment report decentralised procedure: Rosuvastatin. 2001. http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con744443.pdf. Accessed 11 January 2019.

41. Wandera OR. Formulation development of generic rufinamid uncoated tablets. [Ph.D. thesis]: University of Nairobi; 2015.

42. Australian Government Department of Health and Ageing: Australian Public Assessment Report for Sapropterin dihydrochloride. 2011. https://www.tga.gov.au/sites/default/files/auspar-kuvan.pdf. Accessed 7 January 2019.

43. Ono A, Tomono T, Ogihara T, Terada K, Sugano K. Investigation of biopharmaceutical and physicochemical drug properties suitable for orally disintegrating tablets. ADMET DMPK. 2016;4(4):335-60.

44. Visych SY, Dorovskyy O, Andryukova L, Fetisova O. Bioequivalence studies of medicinal products of tranexamic acid. Ukr bìofarm ž. 2016(6 (47)):24-8.

45. Chakraborty S, Yadav L, Aggarwal D. Prediction of in vivo drug performance using in vitro dissolution coupled with STELLA: a study with selected drug products. Drug Dev Ind Pharm. 2015;41(10):1667-73.

46. Endrenyi L, Tothfalusi L. Determination of bioequivalence for drugs with narrow therapeutic index: reduction of the regulatory burden. J Pharm Pharm Sci. 2013;16(5):676-82.

47. Zakowiecki D, Cal K, Kaminski K, Adrjanowicz K, Swinder L, Kaminska E, et al. The improvement of the dissolution rate of ziprasidone free base from solid oral formulations. AAPS PharmSciTech. 2015;16(4):922-33.